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The American Journal of Medicine

Vol. XII JUNE, 1952 No. 6

Editorial

Clinical Studies

The development of commissurotomy for mitral stenosis is one of the most spectacular achievements of cardiovascular surgery and one which imposes upon the internist the full responsibility for understanding the indications and contraindications of surgery in rheumatic heart disease. The authors, whose experience extends to over 400 commissurotomies in the past four years, analyze their experience in this respect in a paper which is most timely and of the greatest interest.

Following finger fracture mitral valvuloplasty in eighteen patients with rheumatic mitral stenosis there was, in general, a significant decrease in the intensity and duration of the apical diastolic murmur and this change augured a good therapeutic result. A Graham Steell murmur, indicative of pulmonic insufficiency, was present in six instances and disappeared postoperatively in all.

Continuous electrocardiographic recordings throughout the entire procedure of finger fracture mitral valvuloplasty disclosed the transient occurrence of a great variety of cardiac arrhythmias at different stages of the operation. The authors report a valuable experience with drugs used to abolish the more serious and persistent of these irregularities; particularly noteworthy is their use of prostigmine.

The development of mitral commissurotomy has pointed up the importance of a clear understanding of the effects of mitral stenosis on the pulmonary and systemic circulation. Until recently investigation along these lines, by cardiac catheterization and other technics, was hampered by the difficulty of measuring left atrial pressure. In the present study the pulmonary "capillary" pressure has been used as an approximation of the pressure in the left atrium and pulmonary veins. Observations made before and after commissurotomy are of special interest.

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in penicillin reactions...

NEW, "remarkably effective"[1] treatment

Decholin (BRAND) Sodium and Decholin (BRAND)

Gratifying results are reported[1-2] with *Decholin Sodium* and *Decholin* in treating penicillin reactions of the most commonly encountered type—with symptoms simulating serum disease. The treatment "has not failed so far in any patient with serum-sickness type of penicillin sensitivity."[1] Most of the patients in this study had been given a variety of other medications without success prior to the successful use of *Decholin Sodium* and *Decholin*.

SYMPTOMS: Fever, itching, joint pains, urticaria, edema, hoarse or tight throat and other serum-sickness types of penicillin reactions respond promptly to this new therapy—relief is usually complete within an average of four days.

TREATMENT: Subject to adjustment by the physician, a routine schedule is to inject 5 cc. *Decholin Sodium* intravenously, once daily or every other day (depending on degree of sensitization), also one tablet of *Decholin* three times daily.

Decholin Sodium (brand of sodium dehydrocholate) 20% aqueous solution for intravenous injection; ampls of 3 cc., 5 cc. and 10 cc.

Decholin (brand of dehydrocholic acid) Tablets 3¾ gr. (0.25 Gm.) in bottles of 100.

Decholin Sodium and *Decholin*, trademarks reg.

1. Pelner, L., and Waldman, S.: Postgrad. Med. *11*:49 (Jan.) 1952.
2. Pelner, L., and Waldman, S.: Am. Pract. *3*:293 (Apr.) 1952.

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The American Journal of Medicine

Vol. XII JUNE, 1952 No. 6

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Therapy for Vascular Headache to Reverse the Physiologic Disturbance

Headache, a problem encountered in all kinds of medical practice, may occur in association with any of a variety of disorders, some organic, others purely functional.

In headaches of organic etiology, e. g. sinusitis, febrile disease, brain abscess — the primary objective is to eliminate the basic disease. Head pain can be relieved temporarily with analgesics, pending diagnosis and definitive treatment.

Functional types of headache present a greater problem, because of the obscure nature of their etiology and their recurrent nature. Among these are:

Migraine (both classical and variant forms)
Tension headache
Psychogenic headache
Histaminic cephalgia

Wolff and his co-workers established that the pain of these headaches is due to disturbance of the tonus of cranial blood vessels — hence the term *vascular headaches.*

The craniovascular changes associated with the several phases of the typical migraine attack are:

Vasoconstriction (Drawing I) — to which the visual prodromata are attributable. It is possible to abort the attack during this phase in all but a few cases. (See treatment below.)

Vasodilatation (Drawing II) — as the vessels lose their tone, exaggerated pulsations set in, resulting in the throbbing pain which characterizes vascular headache. Treatment for the attack is still effective during this phase. (See below.)

Vessel Edema (Drawing III) — if the vasodilation continues for too long, vessel walls become edematous; this changes the character of the pain to a steady, intense aching. The attack can now no longer be checked, even with maximum dosage of specific drugs. *Moreover, sustained headache often induces reflex neck muscle tension, a source of residual pain.*

VESSEL STATE — **ACCOMPANYING SYMPTOMS**

I

PRIMARILY VISUAL DISTURBANCES: SCOTOMAS, HEMIANOPIA, UNILATERAL PARESTHESIA, PHOTOPHOBIA.

SPEECH DISORDERS AND MOOD CHANGES: THESE USUALLY LAST FROM A FEW MINUTES TO AN HOUR.

VASOCONSTRICTION

II

AGONIZING PERIODIC HEADACHE USUALLY LIMITED TO TEMPORAL, FRONTAL OR OCCIPITAL REGIONS.

HEADACHE IS THROBBING IN NATURE AND IS RELIEVED SOMEWHAT BY PRESSURE ON COMMON CAROTID ARTERY.

VASODILATATION

III

THE AGONIZING HEADACHE BECOMES DULL AND STEADY. MAY LAST FOR HOURS OR DAYS.

NAUSEA, VOMITING, DRYNESS OF MOUTH, EXCESSIVE SWEATING AND CHILLINESS MAY OCCUR DURING THIS STAGE.

EDEMA

Therapy: For maximum success, treatment must follow two lines:

1. Relieve the acute attack — of the numerous drugs which have been tried, ergotamine and its derivative preparations have proved most effective. The *newest product is oral tablets* of Cafergot®, N.N.R. (ergotamine with caffeine 'Sandoz'). When dosage is adjusted to the needs of the individual, Cafergot will give good relief in 85% of cases. It enables a greater number of patients to benefit from early administration since the oral route simplifies treatment as compared to parenteral therapy.

Many migraine patients delay taking medication until the attack has reached its height. Explicit dosage instructions may be forgotten unless the patient is made to realize their importance. To help encourage adherence to correct dosage procedure, Sandoz Scientific Department has prepared pads of INSTRUCTIONS as reproduced below.

For.....Date.....

1. Take 2 tablets at first sign of attack.
2. If the attack continues take one additional tablet every half-hour until attack is terminated.
3. Do not take more than 6 tablets for any single attack or more than 10 tablets in any one week.
4. If attack develops more rapidly or is more severe than usual, take 3 or 4 tablets as early as possible.
5. If you notice any change in your symptoms, report to your physician immediately.

.....M.D.

Do not take tablets between attacks.

2. Reduce the frequency of attacks — psychotherapy and regulation of living habits to avoid fatigue and nervous tension are most effective.

Supplies of Instruction Sheets as shown in facsimile above will gladly be sent on request; reprints of recent reports on Vascular headaches are also available.

GENERAL REFERENCES: DeJong, R.: Chicago M. Soc. Bull. *54*: 106, 1951. Friedman, A.: Modern Headache Therapy. St. Louis, C. V. Mosby Co., 1951. Shofstall, C. and Shofstall, W.: J. Kansas M. Soc. *52*: 366, 1951. Wolff, H.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

Sandoz Pharmaceuticals
DIVISION OF SANDOZ CHEMICAL WORKS, INC.
68 CHARLTON STREET, NEW YORK 14, N. Y.

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The American Journal of Medicine

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Review

This interesting group of papers representing an analysis of the experience at the Mallory Institute of Pathology offers several instructive points regarding the specificity of the clinical and pathologic manifestations of nodular intercapillary glomerulosclerosis, and the correlation between clinical and pathologic findings. The renal lesion, if properly defined particularly as to nodularity, character and position of the hyaline deposits, was found to occur only in diabetics. On the other hand, the clinical syndrome, diabetes, albuminuria, edema and hypertension, may occur in the absence of the distinctive renal lesion and the renal lesion may be present without association with characteristic clinical manifestations. The papers include a number of other interesting data and speculations relevant to this controversial subject.

Seminars on Congenital Heart Disease

Dr. Brock here discusses the classification, incidence, morbid anatomy, clinical manifestations, diagnosis and surgical correction of congenital pulmonary stenosis, a condition which is not as uncommon as formerly supposed. The direct operation, pulmonary valvulotomy, introduced by the author, is described and the indications for direct and indirect operations are discussed. Dr. Brock concludes with an analysis of 240 cases of congenital pulmonary stenosis he has operated upon, in eighty-two of which pulmonary valvulotomy was performed. The results become more and more impressive as experience grows.

Combined Staff Clinic

Combined Staff Clinics (Columbia University College of Physicians and Surgeons)—The chemotherapy of cancer has grown out of the purely empirical phase of statistical analysis of the results of treatment and it is now possible to answer, to some extent, certain basic questions as to how and where the chemotherapeutic agents act. It is with such questions and answers, as they relate particularly to the nitrogen mustards and antifolics, that the present Clinic is largely concerned. The Clinic ends with a realistic evaluation of the present status of these agents in cancer therapy.

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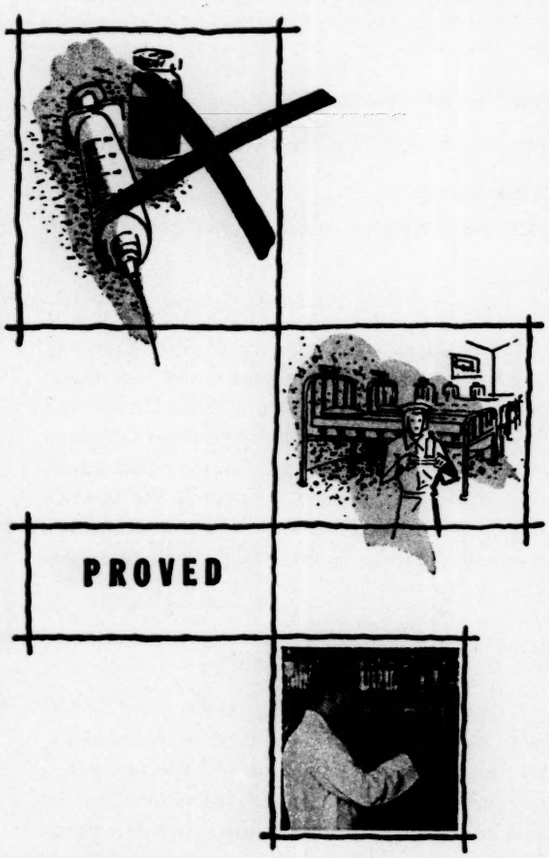
NEW

aminodrox

36 gr. aminophylline a day! . . . **ORALLY**



Aminodrox, a tablet containing colloidal aluminum hydroxide with 1 1/2 or 3 gr. of aminophylline provides what the medical profession has been looking for–a *dependable* method of *oral* administration of aminophylline in doses large enough to produce the same high blood levels obtainable with parenteral administration.

This is possible with Aminodrox because gastric disturbance is avoided.

Several studies* attest to the large dose tolerance of Aminodrox. A dose of 36 grains daily produced blood levels *higher* than would be customarily aimed at with parenteral administration. In hospitalized patients on this excessively massive dosage, only 27 % showed gastric distress. Contrast this to the 42 % intolerance to plain aminophylline with only 12 grains a day. Another group of patients on 15 grains daily of aminophylline–administered as Aminodrox–showed excellent tolerance to this dosage and blood levels well in the therapeutic range hitherto obtainable only by injectable** aminophylline.

Aminodrox now makes it possible to discard the inconvenience and potential hazards of non-emergency parenteral aminophylline. Besides its use as a diuretic, it is now feasible to use *oral* aminophylline therapy in the treatment of congestive heart failure, bronchial and cardiac asthma, status asthmaticus, and paroxysmal dyspnea.

*Cronheim, G., Justice, T. T., and King, J. S., Jr.. A New Approach to Increasing Tolerance of Oral Aminophylline—to be published.

*Justice, T. T., Jr., Allen, G., and Cronheim, G., Studies with Two New Theophylline Preparations—to be published.

**Waxler, S. H. and Schack, J. A., Administration of Aminophylline, J. A. M. A. 143:8, 736-739, June 1950 (This study does *not* refer to Aminodrox.)

aminodrox

for effective oral aminophylline therapy

S.E. Massengill

Bristol, Tennessee

SEND FOR DETAILED LITERATURE

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The American Journal of Medicine

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Clinico-pathologic Conference

Case Report

Notice Concerning Cumulative Index of

THE AMERICAN JOURNAL OF MEDICINE, 1946–1951

As indicated in the December 1951 issue of The American Journal of Medicine, many requests have been received for a cumulative index of the Journal to make the material more accessible for review. In response to these requests, a subject and author index covering the period July, 1946–June, 1951 has been prepared and is now available from the publishers, The American Journal of Medicine, Inc., 49 West 45th Street, New York 36, New York. The cost per copy is $2.50 U. S. A., $3.00 foreign.

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

• Lithograph by Honore Daumier, from the series "Strangers in Paris". Courtesy, Bettmann Archive.

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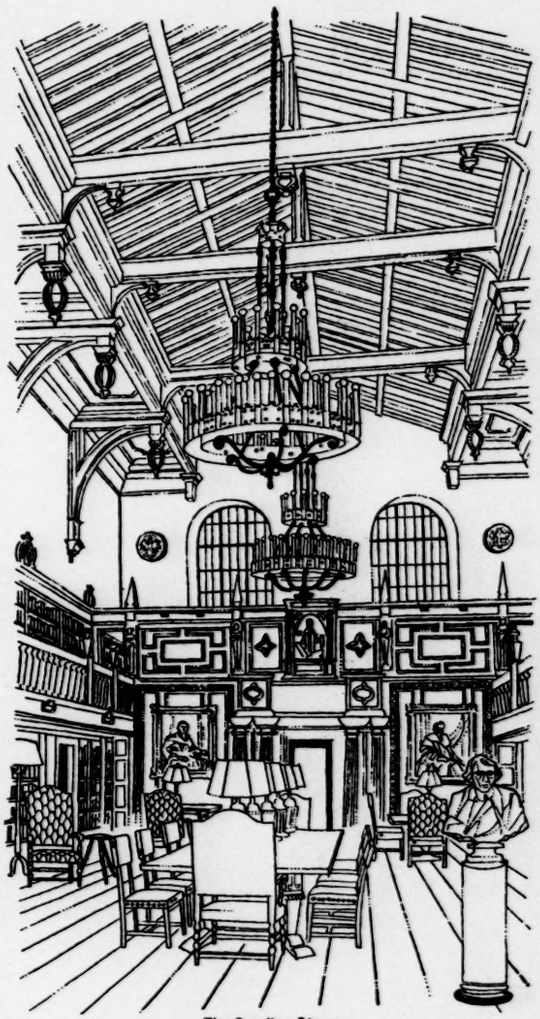

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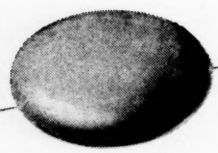
in broad-spectrum therapy



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The appealing flavor of Ovaltine makes it acceptable to children as well as adults, including the aged. Ovaltine in milk is easily digested, an important feature when digestive disturbances are a factor.

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(Each serving made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk)

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COBALT	0.006 mg.	CHOLINE	200 mg.
*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.7 mg.	PANTOTHENIC ACID	3.0 mg.
*IRON	12 mg.	PYRIDOXINE	0.6 mg.
MAGNESIUM	120 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.2 mg.
*PHOSPHORUS	940 mg.	*VITAMIN A	3200 I.U.
POTASSIUM	1300 mg.	VITAMIN B_{12}	0.005 mg.
SODIUM	560 mg.	*VITAMIN D	420 I.U.
ZINC	2.6 mg.		

*PROTEIN (biologically complete)	32 Gm.
*CARBOHYDRATE	65 Gm.
*FAT	30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council.

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*Kramer, P., and Ingelfinger, F. J.: Mid. Clin. North Amer. 32:1227, 1948.

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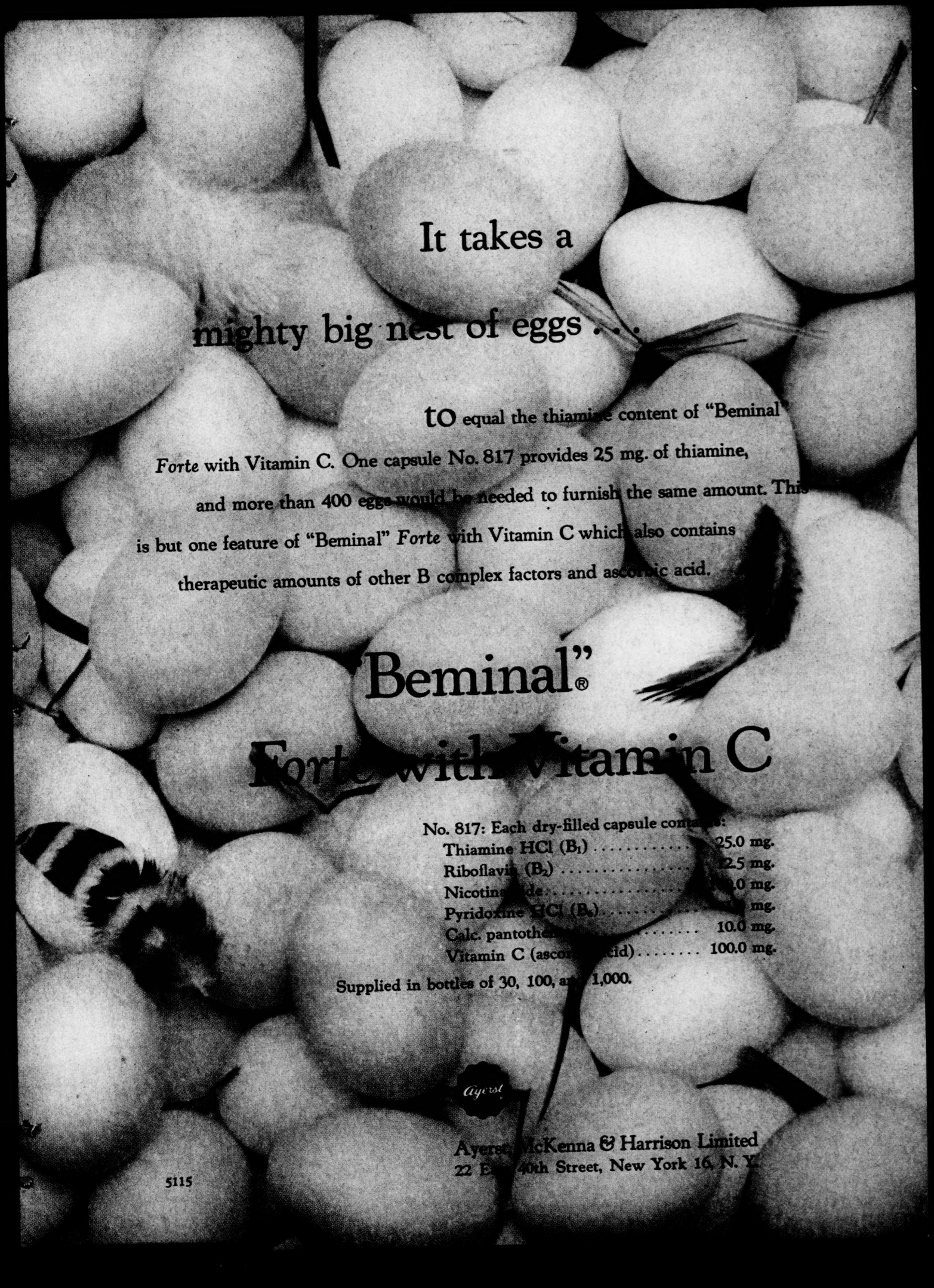
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Hamblen, E. C.: North Carolina M. J. **7**:533 (Oct.) 1946.

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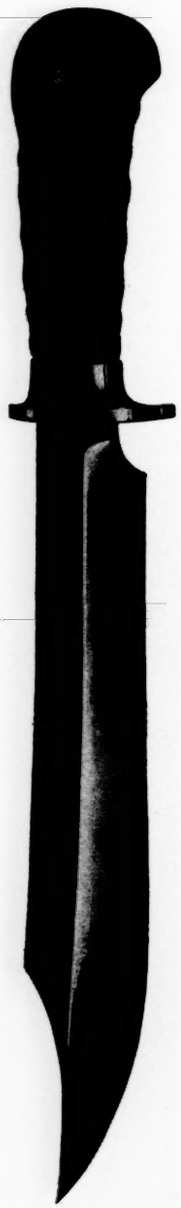

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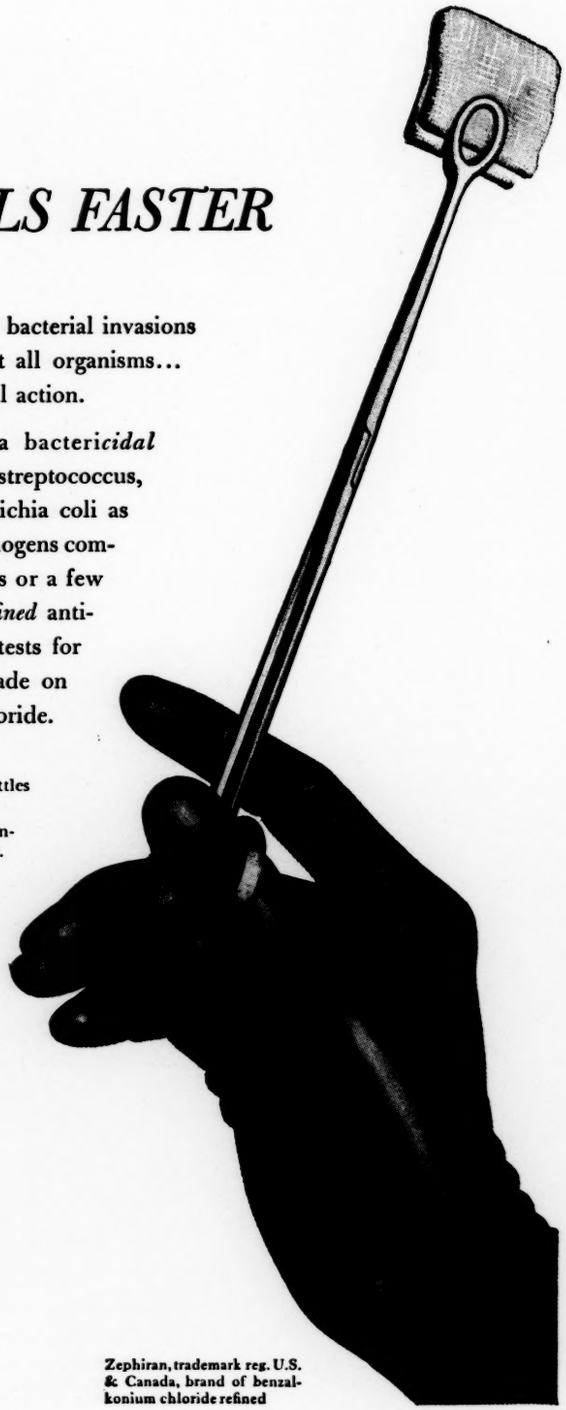
Concentrated Aqueous Solution 12.8%, bottles of 4 oz. and 1 U. S. gallon (1 oz.=1 U. S. gallon 1:1000 solution). Must be diluted.



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Also available: Solution Rubramin Crystalline (Squibb Crystalline Vitamin B_{12} Solution) in 1 cc. ampuls, 15 micrograms of crystalline vitamin B_{12} per ampul, and 10 cc. vials, 30 micrograms of crystalline vitamin B_{12} per cc.

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Antipruritic, soothing, and cooling, CALADRYL quickly relieves the distress of itching skin. The antihistaminic-antipruritic action of this smooth, creamy lotion provides comfort in sunburn, prickly heat, diaper rash, insect bites, poison ivy or poison oak dermatitis, urticaria, and minor skin irritations.

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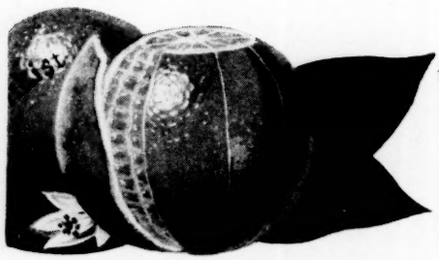
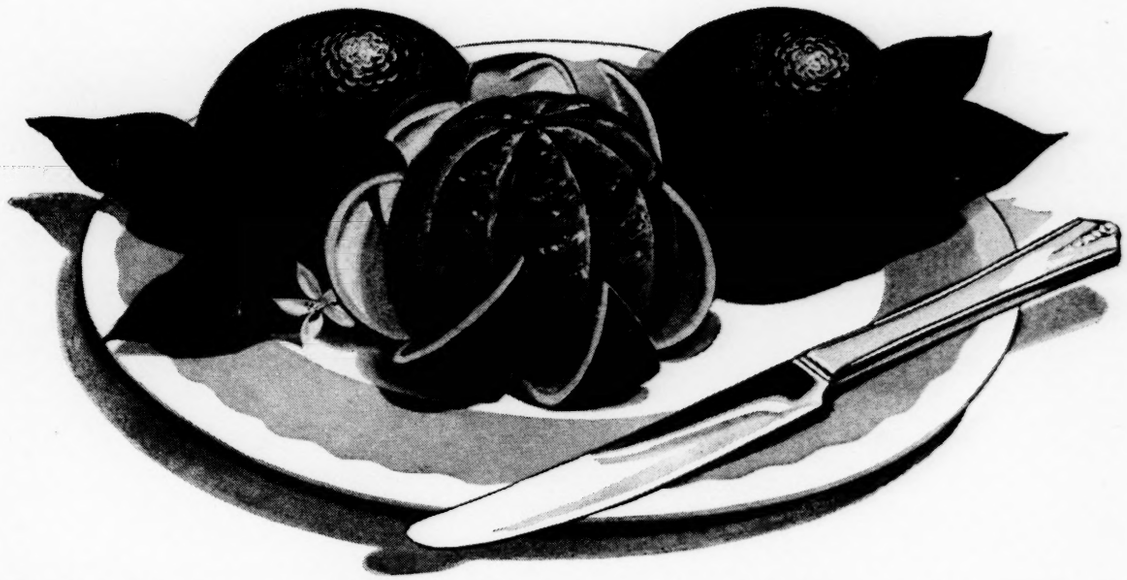


To peel an orange quickly: cut off top, score skin in sixths, and strip off as shown, leaving the valuable white material (albedo) that clings naturally.

Recently rekindled interest again has focused attention on the protopectins, the native form of pectin as it occurs in certain fruits. California oranges supply generous amounts of these complex carbohydrates. In the edible portion of the orange they occur in the fibrovascular bundles, the intersegmental walls, and the juice sacs. Only comparatively small amounts are contained in the juice.

When the fruit is eaten whole, the ingested protopectins are converted to pectin within the small bowel. Subjected here to progressive enzymatic action, and to bacterial action chiefly in the colon, pectin is gradually broken down into substances which to a large extent are responsible for its advantageous behaviour in the intestinal tract.

Eating whole oranges daily can have far-reaching effects on nutritional health and general well-being, accomplished through the promotion of improved intestinal function, a better intestinal environment, and enhanced nutrient absorption.



The beneficial effects of the protopectins begin with the release of pectin into the intestinal contents. Here is what you may look for from the daily ingestion of protopectins as supplied by California oranges, when the fruit —properly peeled—is eaten whole:

A Valuable Two-Way Regulatory Influence

The protopectins help avoid many digestive ills and upsets. They provide a valuable soothing and demulcent influence to counteract the effects of intestinal irritants; thus they aid in the prevention of diarrhea. Their high water-binding power leads to the formation of desirable gelatinous bulk which gently cleanses the intestinal wall and stimulates peristalsis; in this manner the protopectins tend to prevent constipation.

Improved Absorption of Nutrients

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1. Vollmer, H., Pomerance, H. H. and Brandt, I. K.: New York State Med. J., 50:2293, 1950.

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MEAT... and our changing national caloric requirement

Because of labor-saving devices in present-day occupations, automotive transportation, and fewer hours in the working day, and because population concentrations are moving from rural to urban areas, the resulting changes in living habits have sharply decreased the caloric needs of millions of Americans.[1] Whereas many persons formerly expended 3,500 calories or more daily, today their expenditure may be only 2,500 calories per day. Despite this reduction in caloric requirements, the needs for most essential nutrients—proteins, vitamins, and minerals—remain largely unchanged.

Hence, today more than ever before, foods should be chosen for their high content of essential nutrients in relation to the calories they provide. Foods of high nutritive quality, such as meat, therefore, assume particular importance in the changing American diet.

That meat supplies an abundance of essential nutrients in relation to calories is evident from the table given below. Note that the percentage contribution of the recommended daily dietary allowances made by each nutrient is greater or much greater than the percentage contribution made by the calories.

Calories and Nutrients Provided by 6 oz. of Average Cooked Meat and Their Percentages of Recommended Daily Dietary Allowances

	Amounts per 6 oz. of Average Cooked Meat*	Percentages of Recommended Daily Dietary Allowances N.R.C.†
Calories	454	19%
Protein (biologically complete)	44 Gm.	63%
Iron	5.6 mg.	47%
Phosphorus	4.4 mg.	28%
Niacin	9.5 mg.	79%
Riboflavin	0.44 mg.	24%
Thiamine	0.50 mg.	42%

*Average number of calories and average amounts of the chief nutrients furnished by six-ounce servings of cooked meat (averages of amounts furnished by six ounces each of cooked beef, lamb, pork, and veal).[2]

†National Research Council's recommended daily allowances for a sedentary man (154 lb.).

In addition to the nutrients listed above, meat contributes noteworthy amounts of the vitamins biotin, choline, folic acid, inositol, pantothenic acid, pyridoxine, and the newly discovered vitamin B_{12}.

1. King, C. G.: Trends in the Science of Food and Its Relation to Life and Health, Nutrition Rev. *10*:1 (Jan.) 1952.

2. Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared, in Agriculture Handbook No. 8, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, 1950.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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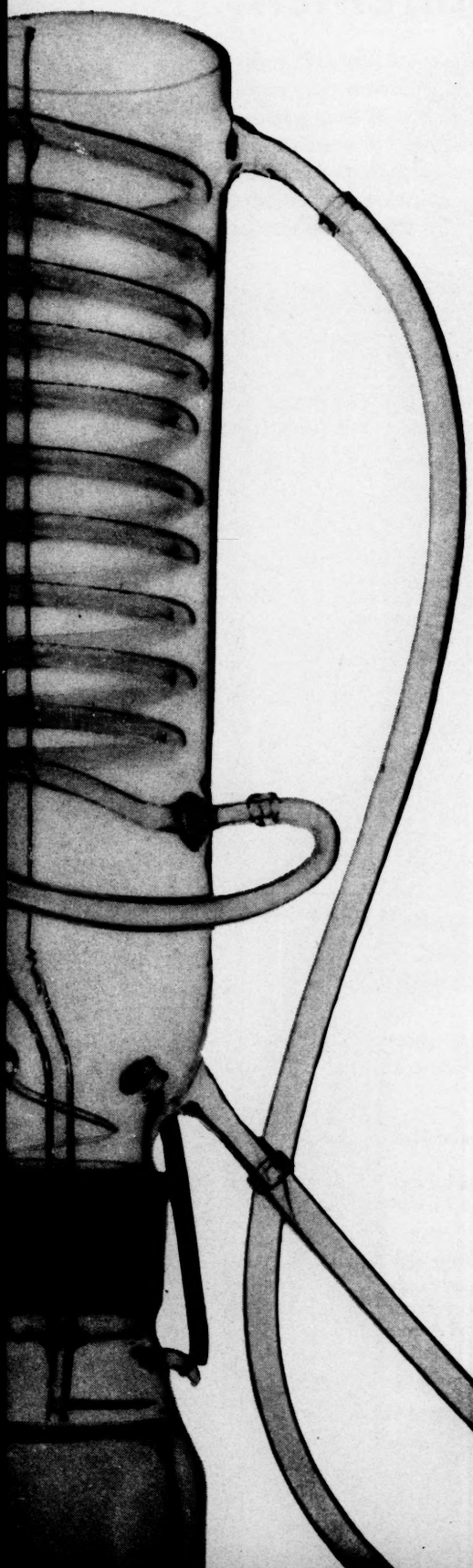

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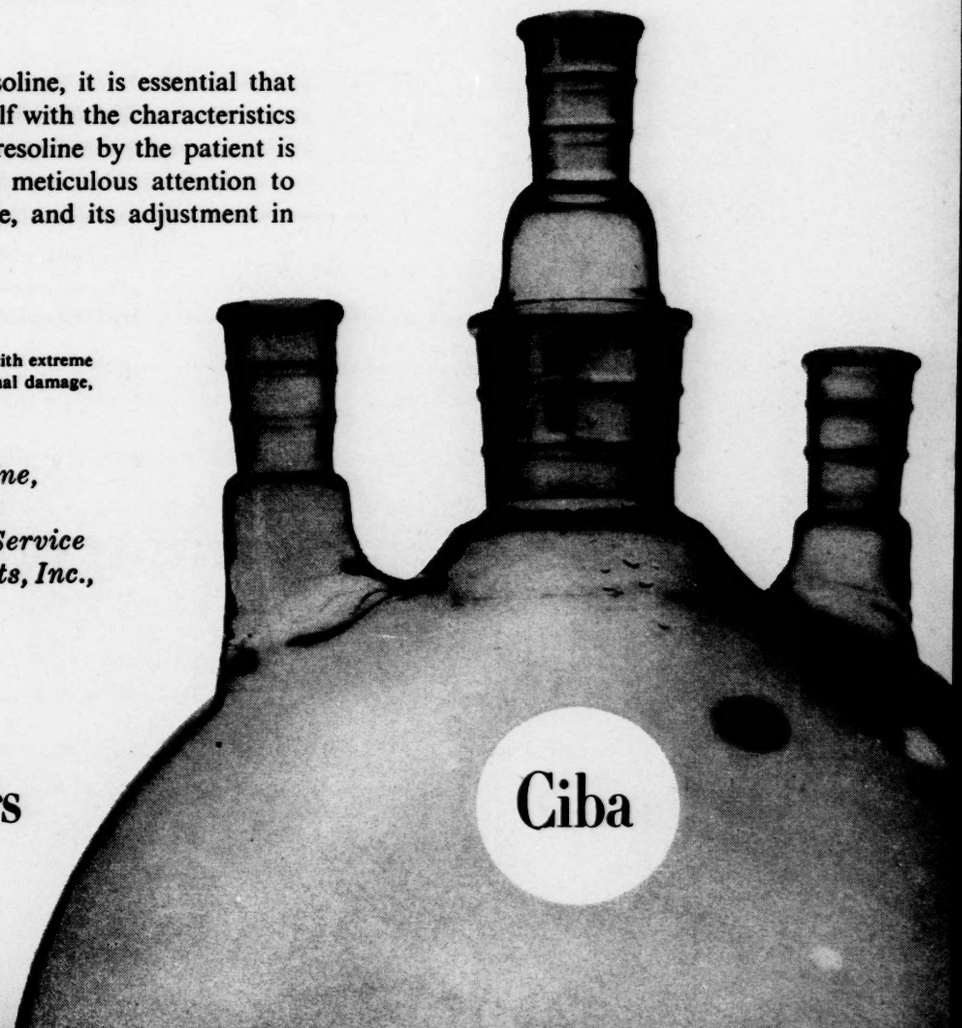
Apresoline, like any hypotensive agent, should be used only with extreme caution in patients with coronary artery disease, advanced renal damage, and existing or incipient cerebral vascular accidents.

For complete information on Apresoline, contact the Ciba Professional Service Representative or write the Medical Service Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.



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bibliography: (1) Couperus, M.: J. Invest. Dermat. *13*:35, 1949. (2) Peck, S. M., and Michelfelder, T. J.: New York State J. Med. *50*:1934, 1950. (3) Soifer, A. A.: Quart. Rev. Int. Med. & Dermat. *8*:1, 1951. (4) Johnson, S. M., and Bringe, J. W.: Arch. Dermat. & Syph. *63*:768, 1951. (5) Hitch, J. M.: Clinical Appraisal of a New Antipruritic (N-ethyl-o-crotonotoluide), to be published. (6) Tobias, N.: G. P. *4*:43, 1951. (7) Domenjoz, R.: Schweiz. med. Wchnschr. *76*:1210, 1946. (8) Patterson, R. L.: South. M. J. *43*:449, 1950. (9) Pierce, H. E., Jr.: J. Nat. M. A. *43*:107, 1951. (10) Hand, E. A.: J. Michigan M. Soc. *49*:1286, 1950. (11) Tronstein, A. J.: Ohio State M. J. *45*:889, 1949.

*U.S. Pat. #2,505,681

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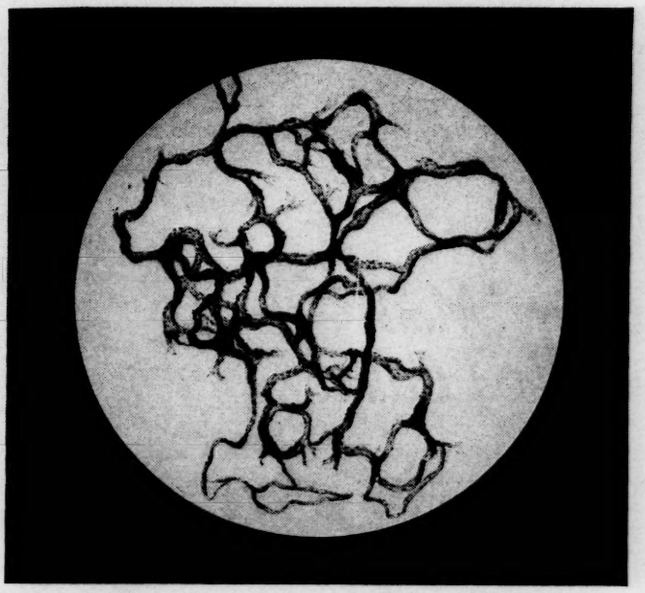

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The American Journal of Medicine

VOL. XII JUNE, 1952 No. 6

Editorial

"The Proper Study of Mankind Is Man"

Alexander Pope

CONVENTIONAL pharmacologic investigations deal chiefly with experiments on laboratory animals. The character of their contribution to knowledge is well known: mechanisms of action, absorption, excretion and several other types of preliminary and basic information. This contribution is of paramount importance in laying the groundwork for the therapeutic use of medicinal agents. There is a specific aspect of pharmacology which needs more widespread attention, namely, that involving investigations with the participation of the patient, clinical pharmacology. Studies with humans are imperative, for without them large gaps remain in the therapeutic structure that cannot be filled with the results from animal experiments alone.

Medicinal agents usually receive some form of testing in patients prior to their release for general use. The term "clinical trial" is the label usually applied to such testing. The clinical trial has become a very busy enterprise in recent years. In a view of the field of clinical trials as a whole one finds much that is sound and informative and much that is otherwise, perhaps an unduly large proportion of the latter. That the issues of clinical trials of agents intended for therapeutics are of markedly varying quality is to be expected since there are differences in the knowledge, skill and experience of those who carry them out. The results relating to quantitative aspects of the therapeutic agents involved are apt to be particularly wanting in reliability in the usual so-called clinical trials.

There is a point in drawing a sharp distinction between the clinical trial and clinical pharmacology. The latter labels a scientific investigation involving specific plans, proper controls, standards for evidence, analysis of data by statistical methods and other guards to help reveal the facts and avoid error. This participation of patients in pharmacologic investigations has not invalidated the need for the laboratory study in animals as a preliminary step. It has increased the problems of introducing new agents into therapeutic use. A special kind of investigator is required, one whose training has equipped him not only with the principles and technics of laboratory pharmacology but also with knowledge of clinical medicine, familiarity with the physical and psychologic reactions of the human patient. A special line of defense is constructed for a study in clinical pharmacology to provide the participating patient with all protection against hazards, such as those of the erroneous drug or improper dosage. Injections of any new medication are made by physician investigators whose experience has placed them high in the ranks of the hospital staff. With patient participants special emphasis is placed in the plan to reduce to a minimum the number of patients required and increase to a maximum the amount of information supplied by each.

Clinical pharmacology is not a new science. Examples are encountered throughout the years. William Withering's painstaking clinical studies on foxglove during a period of about ten years in the latter part of the eighteenth century is, with a few modifications, a fine specimen of it.

The strength of this discipline has manifested itself most clearly in the comparison of therapeutic agents, qualitatively, and more especially quantitatively, the bioassay. A fair number of recent contributions can be cited: studies in the clinical pharmacology of analgesics, curare, cinchona compounds, khellin,® human bioassay of digitalis, comparison of the tolerance of children and adults to members of the digitalis group and bioassay of diuretic agents in ambulant patients with congestive heart failure.

During World War II the shortage of quinidine led to a clinical comparison of quinidine and synthetic dihydroquinidine in the hope of utilizing the latter as a substitute in disorders of cardiac rhythm. An extensive comparison by distinguished clinicians led them to the conclusion that dihydroquinidine was twice as potent as quinidine in man. A subsequent study in clinical pharmacology, a human bioassay, reversed the verdict. It showed that the potencies of the two compounds were indistinguishable in man. Animal experiments showed khellin to be very active in dilating coronary vessels, and several reports of clinical trials agreed that it was effective in controlling the pain of the angina of effort in patients with heart disease. The first study applying the rules of clinical pharmacology discovered that patients could not distinguish khellin from sugar of milk by the effect on their cardiac pain. These results were not hailed with intense enthusiasm, but they appeared to represent the cold facts rather than fervid wishes, and so it is that reports have begun to multiply confirming them.

This is perhaps enough to remove any doubt about the point of this editorial, namely, that clinical pharmacology is a fairly exact science concerned with ascertaining facts about medicinal agents in humans and human patients. These facts may then be used as a basis for treatment of patients, or therapeutics. It would be incorrect to identify clinical pharmacology with either therapeutics or the so-called clinical trial.

Interest in this aspect of biology and medicine has been slow to develop, but it has shown an awakening and accelerated activity in the past few years which, one should hope, will continue to gain momentum.

HARRY GOLD, M.D.

Clinical Studies

Indications for Commissurotomy in Mitral Stenosis

O. Henry Janton, M.D., Robert P. Glover, M.D. *and* Thomas J. E. O'Neill, M.D.
Philadelphia, Pennsylvania

For centuries the therapeutic problems of heart disease, both valvular and myocardial, have been entirely in the province of the internist. With the recent development of intracardiac surgical procedures a major adjunct in the treatment of mitral stenosis has become available. Because this application of surgery to the treatment of structural stenosis of the mitral valve must necessarily undergo much initial conjecture and speculation, it is understandable that the profession for the most part has adopted an attitude of watchful awareness before commitment to a venture so presumably radical. Events have now proved, after a sufficient lapse of time and with a very considerable experience, that this position of reticence is no longer justified. As analysis has shown that the greatest single factor in the successful performance of surgery for mitral stenosis is the proper selection of cases, it would seem fitting to devote considerable attention to this phase of the entire problem.

Sir Lauder Brunton,[1] as early as 1902, was the first to recognize that the only logical method of interrupting the relentless chain of events attendant upon progressive mitral stenosis is that of direct surgical reconstruction of the valve itself. Realizing that drug therapy, effective as it is, is merely the treatment of the effects of this disease rather than the alleviation of its mechanical cause, he, an internist, suggested that direct surgical incision ("lengthening the slit") of the stenotic valve was mandatory. Successive generations of mankind must always be indebted to the brilliance of this revolutionary concept despite the fact that forty-six years elapsed before its proper and successful application was consummated in 1948.[2] It is not the province of this publication to review the painstaking and, at times, fruitless efforts of many investigators,[3–9] including the authors, who have been responsible for the present successful surgical treatment of mitral stenosis by commissurotomy. Many previous reports have detailed the pathologic and physiologic considerations of this valvular deformity and the technical aspects of its surgical correction have been outlined.[10–15]

It is sufficient to state here that mitral commissurotomy is a procedure in which the individual anatomic leaflets of the stenotic mitral valve are surgically separated. By incising the angles, or commissures, of the mitral slit a considerable degree of valve function can be reestablished without the production of additional significant mitral insufficiency. It is to be noted that no valve tissue is removed, thus allowing, insofar as pathologic conditions present will allow, the liberated although thickened valve leaflets to open during ventricular diastole and approximate during ventricular systole. (Fig. 1.)

This operation has been performed by the authors and their former associates in over 400 cases during the past four years. The overall mortality rate in the entire series, including many far advanced, almost terminal cases has been approximately 10 per cent. A mortality rate of under 5 per cent has been maintained in those cases (well over one-half of the entire series) treated at a reasonably early or moderately advanced stage of their disease. Seventy-eight per cent of these patients have obtained "clinical cures" or have been so greatly improved as to return to almost full normal activity with or without medication. Twelve per cent have been unimproved.

It cannot be too strongly emphasized that surgical reconstruction of the permanently damaged valve is but a major adjunct in the continuing care of these rheumatic victims. Although such patients have been restored to a high level of efficiency, and as such can now

enjoy a more normal life, nevertheless they must always be considered as cardiac patients under the watchful care of their attending physicians just as the surgically treated tuberculous patient will require frequent follow-up observation, advice and management. To date

FIG. 1. Diagrammatic representation of the mitral valve cone in the stenotic state. *a*, The right index finger and commissurotomy guillotine in place for initial cut on anterolateral commissure. The anterolateral commissure is opened completely, the posteromedial only partially to avoid encroachment upon the left ventricular out-flow tract. The right index finger (intra-auricular) locates the commissures and guides the proper placement of the knife. Actual cutting is done with the left hand making pressure on the handle of the guillotine blade. *b*, The valve cone partially opened during ventricular diastole; *c*, the valve cone closed, showing reasonable approximation of the cut cusp margins during ventricular systole, thus minimizing mitral regurgitation.

(admittedly an observation of at most four years) there has been no evidence of a return of the stenotic valvular state detectable either clinically, by roentgenograms, electrocardiographic findings, or by long-term physiologic studies (pulmonary artery and right heart pressure studies obtained by cardiac catheterization). These data are at present being published elsewhere.

The selection of patients for commissurotomy, by our present criteria, is to be considered under seven major categories: The history, age of the patient, valvular defect or defects, cardiac size, electrocardiographic findings, functional capacity and complicating factors such as rheumatic activity, arrhythmias and embolic episodes.

1. The typical history is almost invariably one of progressive functional incapacity and repeated episodes of cardiopulmonary embarrassment. Ease of fatigability is a frequent prodromal sign which often may be overlooked by both the patient and physician. Later, fatigue may reach a state wherein the patient is exhausted by the slightest activity, such as combing the hair, shaving or the exertion of going to the bathroom, any of which acts may lead to severe dyspnea and exhaustion. Frequent episodes of paroxysmal nocturnal dyspnea and hemoptysis are commonplace. With failure of the right ventricle, the pulmonary symptoms may be relieved and the course of events is now one of hepatic congestion and discomfort, ankle edema, ascites and the like. Throughout this period a rigid medical regimen is required to keep the patient comfortable. With progression the inevitable malignant chain of events ensues, namely, auricular fibrillation, embolic episodes, gradual helplessness until the patient is in a state of mental and physical dissolution. It is our constant plea that once this malicious and progressive pattern begins to become manifest by the onset of fatigue and early exertional dyspnea that then, and not later, the patient be evaluated for surgical intervention. It is to be remembered that when the symptoms of mitral stenosis begin, the pathologic changes within the stenotic valve itself are already late and may be practically complete. Further progression of the disease complex may well be that of an increasing *symptomatic* series of events, the result of gradual myocardial breakdown and mechanical strain, rather than any further contraction of the already tiny mitral orifice. It must be emphasized, however, that the mere presence of a mitral diastolic murmur without accompanying symptoms is not at this time sufficient reason to suggest surgery. No doubt the day will come in the near future when such a course will seem reasonable. No one today awaits the complications and end results of mechanical de-

formities, such as patent ductus arteriosus or coarctation of the aorta, before proceeding to their surgical correction. On the contrary, it is the accepted operative practice to proceed shortly after the diagnosis has been made clear and long before symptoms and signs of irreversible damage have supervened. Surgery for mitral stenosis at such an early stage would carry an infinitely lower mortality than it does today and much cardiac disability and suffering might be obviated.

2. The natural history of a disease as progressively malignant as mitral stenosis will usually preclude consideration of many patients over the age of fifty. Few patients falling within the limits of the surgical indications as presented herein will be alive after the fourth decade and those who are, as a rule, will have other cardiac complications which would militate against the performance of successful or profitable surgery. This is not invariably true, for chronologic age does not always parallel physiologic age. On occasion, the initial rheumatic affection will occur at a later age than in early childhood and the full-blown picture of mitral stenosis may not then develop until the late forties or early fifties. In other instances, not entirely clear, symptoms are late to develop and only at this late date become manifest to the point of requiring both medical and surgical attention. Such patients are not denied surgery and indeed a number of excellent results have been obtained in this group. It is axiomatic, however, that the older the patient the more rigid should be the criteria of selection and fewer variables should be allowed to influence the physician's judgment. Thus very little deviation from the ideal "pure" stenotic mitral valve candidate would seem to be indicated.

Obviously, as mitral stenosis in all its aspects rarely has time to become prominent before the late teens or early twenties, this problem is primarily one of concern in the young adult through middle age. Our experience, however, has included three cases in children, one at the age of four and two at twelve. As a rule, however, a number of years must elapse between the initial and/or subsequent attacks of rheumatic infection for the pathologic entity of stenosis to become fully formed.

3. The valvular lesion ideally should be that of "pure" mitral stenosis. An associated valvular lesion, be it mitral insufficiency, aortic stenosis or insufficiency, constitutes an absolute contraindication provided they are of sufficient dynamic significance to have expressed themselves by appreciable left ventricular enlargement or a wide pulse pressure. Mitral stenosis, of course, when associated with other valvular malformations, must be the predominant lesion if surgery is to be considered. The predominance in such instances is assured by the historical pattern of progressive cardiopulmonary impairment, a normal sized left ventricle, left atrial and right ventricular enlargement, electrocardiographic evidence of right ventricular preponderance or no axis deviation (never left ventricular preponderance) and evidence of increased pulmonary vascular hypertension either clinical or by actual catheterization measurement.

4. The typical mitral configuration as seen fluoroscopically and by roentgenograms is well known and easily recognizable. It consists of a straightening of the left border of the heart seen on the anteroposterior projection occasioned by the enlargement of the pulmonary artery and the conus segment of the right ventricle. Very little of the left ventricle, except at the extreme apex, is outlined and in the absence of associated valvular deformities this chamber remains relatively normal in size. The right border presents a bulge of the right atrium. Occasionally the left atrium may be of such extreme size as to share in the formation of the right cardiac silhouette.

The least amount of left atrial and right ventricular enlargement is desirable. Left ventricular enlargement should be absent or minimal. Slight enlargement of the left ventricle, due to mitral insufficiency, is not a contraindication to surgery but tends to suggest a more equivocal surgical result. If left ventricular enlargement is due to a dynamically significant aortic valvular lesion, mitral surgery would seem to be contraindicated. An excessive chamber enlargement, such as an aneurysmal dilatation of the left atrium, is a relative contraindication, but exploration of the valve is justifiable. Frequently a greatly enlarged heart will, upon careful observation and analysis, prove to consist entirely of left atrium, right ventricle and right atrium, whereas at first glance the left ventricle would seem to share in the over-all enlargement. Extreme enlargement of all chambers of the heart is an absolute contraindication.

One of our most perplexing problems is the recognition of slight left ventricular enlargement

in the presence of a markedly enlarged right ventricle. With a very considerable experience, the greatly enlarged right ventricle with its clock-wise rotation and subsequent rotation of the left ventricle posteriorly can be detected and appreciated with reasonable accuracy. This problem has required extensive study and deliberation and will form the basis of a subsequent report.

5. The electrocardiogram frequently aids in determining the candidacy of patients having more than one valve defect. Evidence of right ventricular enlargement obviously indicates that the predominant lesion is one of mitral stenosis. A review of the electrocardiographic pattern in the first one hundred consecutive cases revealed that in no instance was there evidence of a left axis shift. Such a finding would indicate that other factors are at play and a careful re-evaluation must follow.

6. The better the functional capacity of the patient the more ideal the candidate. It goes without saying that the best surgical risk is that patient with minimal symptoms of cardiopulmonary incapacity (dyspnea) at normal activity, and that these symptoms be of recent origin. Such a patient usually has minimal cardiac enlargement and a relatively normal electrocardiogram. Our present problem does not lie with this type of individual but rather with the patient who has had symptoms for many years and presents himself with right heart failure, which can be controlled only with the patient at bed rest and on the strictest of medical regimens. Such individuals may have a "pure" mitral stenosis, but the greatly hypertrophied and dilated myocardium has been so damaged by the results of the mechanically strictured valve, and not infrequently by repeated instances of rheumatic carditis, that now irreversible changes are superimposed. If these patients can respond to medical therapy and the congestive failure can be brought under control, the case is acceptable for surgery and, surprisingly, members of this group often are among our most dramatic results. However, one would not expect such individuals routinely to obtain an excellent result and, indeed, they frequently do not. One is usually able, nevertheless, to retard and stabilize their rapid downhill course and to improve the circulation so as to render them much more amenable to medical measures.

7. Mitral stenosis is frequently accompanied in time by many complicating factors that present great additional hazards to the welfare of the patient. One such factor, congestive heart failure, has been discussed. Various arrhythmias are frequent and the most common of these is auricular fibrillation. Auricular fibrillation is by no means a contraindication to surgery *per se* unless the ventricular response is uncontrollable. The presence of auricular fibrillation does not prognosticate a poor result. Over one-half of our patients presented themselves in this category and their eventual result has seemed to suffer little as compared to the group in normal sinus rhythm.

Perhaps the most insidious and distressing insult encountered during the course of this disease is the sudden occurrence of a systemic embolus. The patient may have been in what he considered to be normal health, except for the knowledge of a "heart murmur," only to experience suddenly the shock of an embolus to the brain or extremity. In addition to the clinical residue of such episodes the mental despair and fearful awareness of not being able to prevent or predict the next blow produces such mental chaos that the patient frequently becomes markedly depressed. Commissurotomy offers considerable hope to such people. Such emboli arise primarily from thrombus formation within the left atrium and appendage and the surgical technic entails removal of those within the appendage together with its subsequent ligation and amputation. In addition to the direct removal of thrombi so located and the obliteration of this favorite site, prevention of the future development of thrombi within the left atrium proper is enhanced by alleviation of the factor of stasis when successful enlargement of the mitral orifice with partial restoration of valve function has been accomplished.

The sudden appearance of hemoptysis not infrequently may be the first sign of an underlying stenotic mitral valve hitherto neither suspected or diagnosed. This symptom invariably telegraphs the presence of pulmonary vascular hypertension and, as such, constitutes an urgent indication for mitral commissurotomy usually at a time when a highly satisfactory result can be obtained. Repeated and, at times, massive hemoptysis lends even greater urgency for the initiation of surgical therapy. Hemoptysis may be regarded as direct evidence of pulmonary hypertension, for in forty such cases subjected to cardiac catheterization all showed a con-

siderable elevation of pressure within the vascular bed.

Active rheumatic fever or subacute bacterial endocarditis constitute absolute contraindications for cardiac surgery and need no further discussion.

One of us (T.J.E.O'N.) has prepared the following classification of the stages through which the average case of mitral stenosis will pass. This classification represents an effort to combine a functional and therapeutic yardstick for evaluation of the patient for surgery.

STAGES OF MITRAL STENOSIS

I. Asymptomatic
II. Statically incapacitating
III. Progressively incapacitating
IV. Terminally incapacitating
V. Irretrievable

Stage one includes those with the auscultatory findings of mitral stenosis but who as yet have no symptoms. Cases in *stage two* have progressed to the point at which dyspnea and fatigue under physical stress have developed but the patient, with or without medication, living within his own limitations remains on an even plateau. *Stage three*, inevitably the largest group and one encompassing many variables, includes those who, despite the best medical therapy, are slowly losing ground, i.e., are faced with increasing reliance upon diuretics, daily bed rest, etc. In *stage four*, terminally incapacitating, are those patients in whom there is constant evidence of congestive failure even with reasonably limited physical activity. Most of these can be rendered relatively free of their accumulating tissue fluid only by the strictest of medical regimens, including constant rest in bed. Even then, not infrequently, one is unable completely to reduce hepatic congestion. A certain small percentage of those in this group will ultimately prove after surgery to have been in *stage five* and to have had irreversible pulmonary arteriolar changes. As yet, it has been impossible routinely to separate patients in these two stages by clinical and physiologic methods now available hence we reserve *stage five* to classify those who, despite a technically adequate commissurotomy, receive no improvement because of irreversible cardiopulmonary pathologic change.

To date and rightly so, in this, the initial phases of this surgical investigation, most of the cases referred for surgery have been in categories III, IV and V. It would now seem proper to move up the scale, to eliminate surgery in the irretrievable group (V) and to substitute the statically incapacitating group (II) in greater measure. The asymptomatic group (I) may remain inviolate for the present.

With a greater understanding of the inherent progressive nature of mitral stenosis and the development of an operation which is successful both in lowering mortality rate and in giving highly satisfactory results, the burden of selecting patients at an early stage rests squarely on the shoulders of the practicing physician.

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Clinical Observations in Patients Undergoing Finger Fracture Mitral Valvuloplasty*

I. Auscultatory Changes

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THE unprecedented interest in cardiac surgery among the medical profession at large makes it seem timely to present the auscultatory changes which have been observed in a group of patients undergoing mitral valvuloplasty by the finger fracture technic. Although the recent and fairly extensive experience with mitral valve surgery is only about three years old, it is well to recall that nearly one-half century has passed since surgeons first raised the curtain on the new era of intracardiac surgery. In the intervening years many attempts have been made to attain the goal of these early pioneers.[1–7] However, the courage of these men had to await the development of modern thoracic surgical technics as well as improved methods of anesthesia before the operations could be accepted as more than exciting experiments.

In the past three years Harken, Ellis, Ware and Norman in Boston,[8] Brock, Baker and Campbell in England,[9] Bailey, Glover and O'Neil in Philadelphia,[10] Blalock in Baltimore and many others have perfected their surgical technics and made mitral valvuloplasty a feasible and reasonably safe procedure for selected patients with mitral stenosis. Previous reports have concerned themselves primarily with the technic of surgical approach and the general clinical evaluation of results obtained by the respective groups. To our knowledge no earlier report has been made in the literature specifically evaluating the auscultatory changes in a group of patients undergoing mitral valve surgery.

MATERIAL AND METHODS

The patients constituting the clinical material for this study were all hospitalized on the medical and surgical services of the Peter Bent Brigham Hospital and were closely observed medically through their preoperative and postoperative courses. The initial impression was recorded approximately one week preoperatively after several observations had been made. Convalescent status was evaluated after several examinations from the tenth to the fourteenth postoperative days. This series does not involve the total experience with patients undergoing mitral valvuloplasty in this institution but only that group in whom the auscultatory findings were recorded by one observer (R. J. S.) during the pre- and postoperative period. Clinical improvement was judged as being poor, fair, good or excellent in terms of subjective change in dyspnea, cough, palpitation, precordial fullness and discomfort, as well as by an objective appraisal of orthopnea, vital capacity, exercise tolerance, tachycardia, appetite and so forth.

The murmurs have been graded according to the classification described by Levine and Harvey.[11] In this system the intensity of murmurs is recorded as follows: grade I, the faintest murmur that can be heard after careful auscul-

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tation for a few seconds; grade II, a slight murmur that is heard immediately; grade III, a murmur of intermediate intensity; grade IV, a murmur of intermediate intensity; grade V, the loudest murmur that is still inaudible when the stethoscope is removed from the chest; grade VI, an extremely loud murmur that can be heard with the stethoscope just removed from the chest wall.

TABLE I

Patient	Diagnosis	Age and Sex	Rhythm	New York Heart Association Classification
I. B.	Rheumatic heart disease, mitral stenosis, aortic stenosis, aortic insufficiency	40, M	Auricular fibrillation	III
J. C.	Rheumatic heart disease, mitral stenosis	39, M	Auricular fibrillation	III
C. E.	Rheumatic heart disease, mitral stenosis, mitral insufficiency, ? pulmonic insufficiency	33, M	Auricular fibrillation	III
P. L.	Rheumatic heart disease, mitral stenosis, mitral insufficiency, aortic stenosis	24, M	Normal sinus rhythm	III
M. B.	Rheumatic heart disease, mitral stenosis, mitral insufficiency	46, F	Auricular fibrillation	IV
M. F. C.	Rheumatic heart disease, mitral stenosis, ? tricuspid insufficiency, ? pulmonic insufficiency	34, F	Normal sinus rhythm	III
M. C.	Rheumatic heart disease, mitral stenosis, ? pulmonic insufficiency	42, F	Auricular fibrillation	III
M. DiS.	Rheumatic heart disease, mitral stenosis, ? pulmonic insufficiency	24, F	Normal sinus rhythm	III
M. G.	Rheumatic heart disease, mitral stenosis, mitral insufficiency	46, F	Auricular fibrillation	IV
M. L. G.	Rheumatic heart disease, mitral stenosis, mitral insufficiency	28, F	Auricular fibrillation	III
D. J.	Rheumatic heart disease, mitral stenosis	45, F	Auricular fibrillation	III
R. L.	Rheumatic heart disease, mitral stenosis	28, F	Normal sinus rhythm	III
A. M.	Rheumatic heart disease, mitral stenosis	43, F	Auricular fibrillation	III
A. L. M.	Rheumatic heart disease, mitral stenosis	38, F	Normal sinus rhythm	III
D. M.	Rheumatic heart disease, mitral stenosis, mitral insufficiency, ? pulmonic insufficiency	40, F	Auricular fibrillation	III
J. S.	Rheumatic heart disease, mitral stenosis, mitral insufficiency	43, F	Auricular fibrillation	III
N. W.	Rheumatic heart disease, mitral stenosis, ? pulmonic insufficiency	40, F	Normal sinus rhythm	III
V. W.	Rheumatic heart disease, mitral stenosis	40, F	Normal sinus rhythm	III

Cardiac catheterization was performed in the laboratory of one of us (L. D.) in several of these patients pre- and postoperatively and made a more exact physiologic and clinical correlation possible in this group.

All operations were performed by Dr. Dwight E. Harken by the technic of finger fracture mitral valvuloplasty.[12]

Table I presents in tabular form an analysis of the patients reported in this series. The group comprises eighteen patients of whom four were males and fourteen females. The average age of the male group was thirty-four years (twenty-four to forty) and of these one was in normal sinus rhythm and three had auricular fibrillation. All four men had classical auscultatory findings of mitral stenosis, and in two mitral insufficiency was also present. Aortic valvular involvement was present in two, and pulmonary insufficiency was suspected in one (Graham Steell murmur).

The female series was composed of eight patients with auricular fibrillation and six patients with normal sinus rhythm, the average age being thirty-eight years (twenty-four to forty-six). All of the women also presented classical auscultatory evidence of mitral stenosis, nine having "pure mitral stenosis" and five having mitral insufficiency associated with the stenosis. None of the female patients had clinically detectable aortic valvular disease; however, pulmonic insufficiency was suspected in five (Graham Steell murmur) and tricuspid insufficiency in one.

Observations. The following signs were evaluated:

A. Murmurs
   - Mitral stenosis
   - Mitral insufficiency
   - Pulmonary insufficiency (Graham Steell murmur)

B. Sounds
   - S_1 (apical first sound)
   - P_2 (pulmonary second sound)

C. Thrill
   - Apical diastolic

It should be noted that observations in this preliminary report were limited to the factors associated with the mitral stenosis only, and consideration was not given to aortic or tricuspid lesions.

Results. Table II presents a detailed analysis of the changes recorded in this group of eighteen candidates successfully undergoing finger fracture mitral valvuloplasty.

The diastolic mitral rumble decreased in all patients and disappeared in two. The murmur of mitral insufficiency, where it previously existed, decreased in four of seven, remained the same in three and appeared for the first time postoperatively in nine of these eighteen patients. The murmur of mitral insufficiency, when present preoperatively, was never found to increase in intensity. The Graham Steell murmur was present in six of eighteen patients and disappeared postoperatively in all of these. A new basilar systolic murmur appeared at the

TABLE II

Patient	Grade of Murmur of						Grade of Systolic Murmur Pulmonic Area		Intensity of						Clinical Results
	Mitral Stenosis		Mitral Insufficiency		Pulmonic Insufficiency				S_1 Apical First Sound		P_2 Pulmonic Second Sound		Presence of Apical Diastolic Thrill		
	A*	B*	A	B	A	B	A	B	A	B	A	B	A	B	
I. B.	IV	II	0	II	0	0	0	0	Incr.	Same	Split P2 > A2	Split P2 > A2	0	0	Good
J. C.	IV+	I	0	III	0	0	0	0	Incr.	Same	Split P2 > A2	Split P2 > A2	+	0	Fair
C. E.†	II	I+	III	I	I	0	0	II	Incr.	Same	Split P2 > A2	Split P2 = A2	0	0	Excellent
P. L.	III	I	III	I+	0	0	0	0	Incr.	Same	Split P2 > A2	Split P2 > A2	0	0	Excellent
M. B.‡	I+	I	II	0	0	0	0	0	Incr.	Less	Split P2 > A2	Split P2 > A2	0	0	Good
M. F. C.	IV	I+	0	II+	II	0	0	III	Incr.	Less	Split P2 > A2	Split P2 > A2	+	0	Excellent
M. C.	IV	I	0	II	II	0	0	0	Incr.	Same	Split P2 > A2	Split P2 > A2	+	0	Good
M. DiS.	IV	I	0	0	II	0	0	0	Incr.	Less	Split P2 = A2	Split P2 = A2	0	0	Excellent
M. G.	III	I+	IV	IV	0	0	0	0	?§	?§	Split P2 > A2	Split P2 > A2	0	0	Good
M. L. G.	IV	II	II+	II	0	0	0	0	Incr.	Same	Split P2 > A2	Split P2 > A2	0	0	Good
D. J.	III	0	0	II	0	0	0	0	Incr.	Same	Split P2 > A2	Split P2 > A2	0	0	Excellent
R. L.	III	0	0	I	0	0	0	II	Incr.	Same	Split P2 > A2	Split P2 = A2	0	0	Excellent
A. M.	III	I	0	II	0	0	0	0	Incr.	Same	Split P2 = A2	Split P2 = A2	+	0	Excellent
A. L. M.	III+	I	0	I	0	0	0	II	Incr.	Same	Split P2 > A2	Split P2 > A2	+	0	Excellent
D. N.†	IV	II	IV	III	I	0	0	0	?§	Incr.	Split P2 > A2	Split A2 > P2	+	0	Good
J. S.	III	I	I+	1+	0	0	0	0	Incr.	Same	Split P2 > A2	Split P2 > A2	0	0	Excellent
N. W.†	IV	II	0	0	I	0	0	II+	Incr.	Same	Split P2 > A2	Split P2 > A2	+	0	Excellent
V. W.†	IV	II−	0	III	0	0	0	0	Incr.	Less	Split P2 > A2	Split P2 > A2	0	0	Poor

* A = preoperatively; B = postoperatively.
† Patient studied by cardiac catheterization.
‡ Patient underwent reoperation for residual mitral stenosis via pulmonary vein approach.
§ Systolic murmur obliterates S_1.

pulmonic area in five of these cases, being of grade II intensity in four and grade III intensity in one.

The intensity of the first sound (S_1) was little affected by this procedure, it being decreased in only four of the eighteen. The intensity of the pulmonic second sound was similarly little modified, remaining the same in sixteen and being somewhat reduced in two. In all cases, both pre- and postoperatively, the basal second sounds remained split.

The apical diastolic thrill was noted preoperatively in seven cases and disappeared in all postoperatively.

Phonocardiographic records were obtained in many of these patients pre- and postoperatively to confirm graphically the clinical observations recorded. There are many intrinsic difficulties in securing exactly comparable tracings at widely separated periods of time. Figure 1, however, reproduces a rather characteristic pre- and postoperative phonocardiographic comparison which well illustrates the auscultatory changes in the mitral murmur.

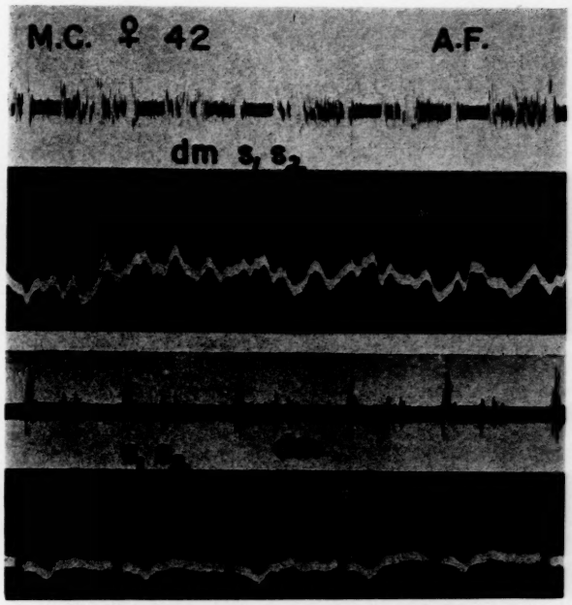

FIG. 1. Upper tracing: preoperative ballistocardiogram and phonocardiographic recording of the mitral diastolic murmur taken at the apex. Lower tracing: postoperative electrocardiogram and phonocardiographic recording at the apex illustrating the decrease in the mitral diastolic murmur, the phonocardiographic controls being identical with those in the upper tracing.

COMMENTS

All of the eighteen patients who are the subject of this report successfully withstood the operative procedure and significant cardiac auscultatory changes were noted in each postoperatively.

Within certain limitations the intensity of the diastolic murmur parallels the severity of mitral stenosis in its evolution,[13,14] and our findings suggest that its postoperative decrease paralleled the clinical improvement of the patient.

Mitral valvuloplasty produced a decrease in the intensity of the diastolic mitral murmur in each of the eighteen cases described. Although the series is small and does not yield itself well to statistical evaluation, the inference is plain that the best clinical result will be obtained in those cases demonstrating the greatest postoperative decrease in the mitral diastolic rumble. Exception must be taken to this statement if the decrease in the mitral diastolic murmur is associated with the onset of a murmur of mitral insufficiency of grade III intensity or greater, as represented by the only cases in this series to show a fair and a poor result. Each of these two patients demonstrated an increase in cardiac silhouette roentgenographically. The postoperative appearance of an apical systolic murmur of grade II or less intensity in some of these patients was well tolerated clinically. Whether or not the postoperative appearance of a grade I or II apical systolic murmur actually indicated the production of mitral insufficiency is a moot point.

In those cases clinically evaluated postoperatively as presenting excellent results the average decrease in the mitral diastolic murmur was 2.3 grades; in those evaluated as good there was a decrease of 1.8 grades. In other cases not evaluated in this report the authors have noted several instances of poor clinical results in patients showing little or no decrease in the mitral diastolic murmur postoperatively.

Our experience with these and other cases reveals that an apical systolic murmur may exist with definite mitral stenosis without evidence of mitral insufficiency being detected by cardiac catheterization[15] or by the surgeon at the time of operation. In some of these instances tricuspid insufficiency has been present.

The early soft blowing diastolic murmur heard in the second and third intercostal spaces to the left of the sternum and following an altered pulmonary second sound was considered indicative of pulmonic insufficiency (Graham Steell murmur) in six of these patients. It disap-

peared postoperatively in all of these instances despite the fact that the pulmonary second sound decreased in only one of these cases. It would seem, therefore, that the loss of the Graham Steell murmur is a more sensitive index of decreased pressures within the pulmonary arterial circuit than the altered P2. The presence of the Graham Steell murmur in one-third of the patients in this series suggests that this murmur is more often met with in severe mitral stenosis than is commonly appreciated.

No explanation seems readily apparent for the appearance of a grade II or grade III systolic murmur noted postoperatively in the pulmonic area in five patients.

The loud snapping apical first sound (S_1) so commonly noted on auscultation in mitral stenosis was present preoperatively in all members of this series except for two instances in which S_1 was incorporated into the apical systolic murmur. Operation changed this physical sign very little.

An apical diastolic thrill was met with on seven occasions, always in association with a murmur of grade III or greater intensity. It disappeared postoperatively in all cases.

SUMMARY

1. The auscultatory findings in eighteen patients with severe rheumatic mitral stenosis are reported before and after finger fracture mitral valvuloplasty.

2. Significant auscultatory changes were noted in all patients postoperatively.

3. In general, significant decrease in the apical mitral diastolic murmur was the best clinical index to expected postoperative improvement.

4. Absence of a decrease in the apical mitral diastolic murmur or development of an operative apical systolic murmur of grade III intensity or greater was generally prognostic of a poor postoperative result.

5. The murmur of pulmonic insufficiency was present in six of the eighteen cases comprising this report and disappeared postoperatively in all of these.

Acknowledgment: Dr. Dwight E. Harken performed mitral valvuloplasty on all of the patients herein reported and we are deeply indebted to him for this close affiliation and for permission to study these patients both pre- and postoperatively. Dr. Samuel A. Levine has been a constant source of inspiration and encouragement. We are grateful to Dr. James Wilson for his help in the recording of the phonocardiograms. The secretarial assistance of Miss Barbara Johnson and Miss Janice Young is gratefully acknowledged.

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Clinical Observations in Patients Undergoing Finger Fracture Mitral Valvuloplasty*

II. Electrocardiographic Observations

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PREVIOUSLY published reports of electrocardiographic activity during intracardiac surgery on human beings has been rather limited[1,2] although there are several excellent papers presenting arrhythmias related to the anesthetic or to extracardiac intrathoracic procedures.[3–7] The changes observed have fallen largely into two main categories: (1) arrhythmias and (2) alteration in the form of the electrocardiogram suggesting left- or right-sided damage and attributed to ischemia, trauma or displacement of the heart.

With the growth of an active medical-surgical unit at the Peter Bent Brigham Hospital dealing with the operative relief of mitral stenosis by finger fracture valvuloplasty, an unusual opportunity has presented itself for studying the electrocardiographic changes associated with this particular form of intracardiac surgery. This paper will present in a brief clinical form the changes observed during surgery where there has been the closest liaison between surgeon, anesthetist and electrocardiographer.

In our presentation three points are chosen for particular emphasis: (1) a statistical analysis of all arrhythmias encountered, (2) a correlation between operative procedures and the associated alterations in the electrocardiogram and (3) a brief discussion of medications found to be useful in the correction of acute surgical arrhythmias.

MATERIAL AND METHODS

Twenty-four candidates for finger fracture mitral valvuloplasty were selected for careful analysis of the associated electrocardiographic changes. This was only a small portion of the total experience of this clinic but represented those cases in which one observer (R. J. S.) was responsible for all the electrocardiographic tracings, having in mind a careful correlation between all operative procedures and the electrocardiogram at the time of surgery.

The patients who constituted this group were hospitalized in the Peter Bent Brigham Hospital and operated on by Dr. Dwight E. Harken.[8] Dr. William Derrick administered all anesthesias. Induction was initiated with pentothal and completed with nitrous oxide, ether and oxygen. Anesthesia was continued by means of ether and oxygen. Morphine sulfate without atropine was given as routine premedication. A Sanborn direct-writing Viso-cardiette machine was used for recording all electrocardiograms. The three standard limb leads and three unipolar limb leads were taken pre- and postoperatively in all cases while continuous operative tracings were recorded using standard limb lead II. The electrocardiographic machine was situated on the floor of the operating room, making possible close correlation between the cardiographer and all surgical and anesthetic procedures being performed.

There were twenty female and four male patients in this series. The average age of the female population was thirty-four years (twenty-four to forty-eight), and of these, seven were in normal sinus rhythm and thirteen had auricular fibrillation. The average age of the male group

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was thirty-three years (twenty-four to forty). One of the four was in normal sinus rhythm and the remaining three had auricular fibrillation.

All patients were taking some form of digitalis at the time of operation except for one case (M. D.), a young woman in normal sinus rhythm.

TABLE 1

INCIDENCE, CLINICAL EFFECT AND THERAPY OF COMMONLY ENCOUNTERED ARRHYTHMIAS IN TWENTY-FOUR PATIENTS

Arrhythmia	Incidence	Clinical Effect of Arrhythmia	Spontaneous Cessation	Arrhythmia Requiring Treatment	Medication Given	Effect of Treatment
Tachycardia (130+)						
Normal sinus rhythm	4	Hypotension 3	1	3	Prostigmine I.V.	Good in all
Auricular fibrillation	15	Hypotension 12	2	13	Prostigmine I.V.	Good in all
Auricular ectopic beats	19	None	All	None	None	.....
Paroxysmal auricular tachycardia	2	None	Both	None	None	.....
Auricular flutter	2*	None	1	1	Prostigmine	Reversion to auricular fibrillation
Paroxysmal auricular fibrillation	1	Hypotension	None	1	Prostigmine	Reversion to normal sinus rhythm
A-V dissociation	3	None	All	None	None	.....
Ectopic nodal beats	12	None	All	None	None	.....
Nodal tachycardia	2	None	All	None	None	.....
Ventricular ectopic beats	24	None	21	3	Pronestyl I.V.	Abolished
Ventricular ectopic beats with bigeminy	11	None	9	2	Pronestyl I.V.	Abolished
Paroxysmal ventricular tachycardia	4	Hypotension 2	2	2	Pronestyl I.V.	Abolished
Ventricular fibrillation †	3	Shock	None	3	Pronestyl I.V. (3); local procaine (1)	No effect (2); reversion to normal sinus rhythm (1)
Cardiac arrest ‡	2	Death	0	2	$CaCl_2$, 10% intracardiac (2)	Ventricular ectopic beats in bursts
Cardiac arrest †‡	1	Shock	0	1	Adrenalin 1:1000 intracardiac	No effect

* Both patients originally in auricular fibrillation
† See text for detailed therapy in successfully reverted case
‡ Following ventricular fibrillation

Observations. Table 1 presents the incidence, clinical effect and therapy of the commonly encountered arrhythmias in this series. The arrhythmias have been listed according to their anatomic site of origin, beginning with the simple sinus tachycardia originating in the sinoauricular node, on through the various types of supraventricular conduction abnormalities, to those of nodal and finally ventricular origin.

In four patients in normal sinus rhythm and fifteen with auricular fibrillation tachycardia of 130 beats per minute or greater developed during anesthesia or the surgical procedure itself. Three of the four in normal sinus rhythm and twelve of the fifteen with auricular fibrillation became hypotensive (80/60) concomitant with the onset of the tachycardia. Spontaneous cessation of the tachycardia occurred in one

patient with sinus mechanism and in two of the fibrillators; however, the remaining three and thirteen patients in the respective groups were effectively controlled with intravenous prostigmine methyl sulfate.

Ectopic auricular beats developed in nineteen patients and two had bouts of paroxysmal tachycardia. Both of these conditions were self-limited, producing no remarkable clinical effect and requiring no treatment.

In two cases auricular fibrillation was replaced by auricular flutter. There was no significant change in the vital signs associated with this arrhythmia. One case reverted to auricular fibrillation spontaneously; the other did so after administration of intravenous prostigmine.

Another patient became hypotensive during a bout of paroxysmal auricular fibrillation but a normal sinus rhythm was promptly restored after intravenous prostigmine was administered.

Atrioventricular dissociation was observed in three instances, ectopic nodal beats in twelve and nodal tachycardia in two. None of these arrhythmias produced any obvious clinical effect and spontaneous cessation occurred in all of them.

The most common arrhythmia encountered during intracardiac surgery was the occurrence of ventricular ectopic beats. These appeared in all twenty-four cases and were coupled, or in bigeminal form, in eleven. Spontaneous cessation took place in twenty-one of the former group and in nine of the latter. The remaining patients received intravenous pronestyl with complete abolition of the abnormal beats.

Paroxysmal ventricular tachycardia was observed in four cases and produced hypotensive effects in two of these. Spontaneous cessation occurred in two cases and intravenous pronestyl abolished the arrhythmia in the others.

Ventricular fibrillation developed in three patients during the operative procedure. Two of these cases terminated with cardiac arrest despite intravenous pronestyl. The intracardiac injection of 10 per cent $CaCl_2$ into the asystolic hearts resulted in a few bursts of ventricular ectopic beats whereas the intracardiac injection of 1:1000 adrenalin had no demonstrable effect.

The third case of ventricular fibrillation also failed to respond to intravenous pronestyl but reverted to normal sinus rhythm following the local bathing of the epicardium with procaine. However, direct massage of the heart was also carried out and intracardiac adrenalin administered.

In Table II an attempt has been made to relate electrocardiographic abnormalities described in Table I to the operative procedure. It should be recalled that all of these patients were under general oxygen-ether anesthesia and furthermore that procaine intercostal nerve block was performed in approximately 30 per cent of the cases before rib spreading was carried out.

TABLE II

ELECTROCARDIOGRAPHIC ABNORMALITIES CORRELATED WITH OPERATIVE PROCEDURES IN TWENTY-FOUR CASES

Operative Procedure	No Electrocardiographic Changes	Tachycardia	Bradycardia	Auricular Ectopic Beats or Tachycardia	A-V Dissociation	Ectopic Nodal Beats	Ventricular Ectopic Beats or Tachycardia	Bigeminy (Ventricular Ectopic Beats)	Ventricular Fibrillation
Endotracheal intubation	13	11	0	0	0	0	0	0	0
Rib spreading*	20	1	1	1	1	0	0	0	0
Pericardial incision	19	0	0	1	0	0	4	0	0
Clamping of auricle	19	0	0	4	0	0	1	0	0
Auricular sutures	5	0	0	19	0	0	2	0	0
Auricular appendectomy	18	0	0	6	0	0	1	0	0
Palpation of ventricular epicardium	13	0	0	0	0	0	11	2	0
Finger in auricle	9	2	0	5	1	2	6	2	0
Palpation of ventricular endocardium	2	7	0	0	0	3	22	0	0
Valve fracture	0	5	2	0	0	4	24	0	0
1–5 min. after valve fracture	2	13	2	0	1	3	20	7	3

* Procaine intercostal nerve block performed in approximately 30% of cases before rib spread

Endotracheal intubation produced no change in thirteen cases, but tachycardia in eleven.

Rib spreading, a comparatively benign procedure relative to the electrocardiogram at least, was accompanied by four abnormal tracings in different individuals, namely, tachycardia, bradycardia, ectopic auricular beats and atrioventricular dissociation.

Incision into the pericardial sac produced auricular ectopic beats in one and ventricular ectopic beats in four.

Manipulation of the auricle resulted in many evidences of ectopic auricular conduction and in few instances of a disturbance of ventricular mechanism. Coincident with the clamping of the auricle, four patients had multiple auricular ectopic beats and one showed ventricular ectopic beats. The placing of auricular sutures resulted in auricular ectopic beats in nineteen and ventricular ectopic beats in two. The act of resecting the auricular appendage resulted in

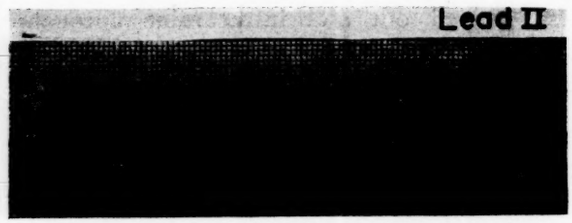

FIG. 1. Typical transient electrocardiographic changes during finger fracture mitral valvuloplasty.

auricular ectopic beats in six and ventricular ectopic beats in one.

Palpation of the ventricular epicardium produced no electrocardiographic change in thirteen, ventricular ectopic beats in eleven and ventricular bigeminy in two.

When the surgeon placed his finger in the auricle prior to valve fracture, the widest range of electrocardiographic abnormality resulted. Nine patients showed no change, two a simple tachycardia, five had auricular ectopic beats, one an atrioventricular dissociation, two ectopic nodal beats, six ventricular ectopic beats and two bigeminy.

During palpation of the ventricular endocardium only two patients failed to show electrocardiographic change. Sinus tachycardia developed in seven patients, ectopic nodal beats in three and ventricular ectopic beats in twenty-two.

During the valve fracture no patient was free of electrocardiographic abnormality. All twenty-four had ventricular ectopic beats, five sinus tachycardia, two bradycardia and four ectopic nodal beats. Figure 1 shows a typical "benign" response to the act of valve fracture.

One to five minutes after valve fracture two of our patients had tracings similar to their preoperative appearance. A tachycardia persisted in thirteen and occasional ventricular ectopic beats in twenty. Two of the electrocardiograms exhibited bradycardia, one atrioventricular dissociation, three showed ectopic nodal beats, seven bigeminy and three ventricular fibrillation (two of which terminated fatally, one being reverted to normal sinus rhythm). Figure 2 is an interesting example of the wide range of arrhythmias that may be encountered in a given patient during surgery. Here normal sinus rhythm, atrioventricular dissociation, ventricular flutter, ventricular fibrillation and again return to normal sinus rhythm are observed.

The third objective of this paper is to report our experience with certain drugs found useful

TABLE III
USEFUL DRUGS

Drug	Route of Administration and Dose	Indications for Use	Effect	Times Drug Used
Pronestyl	200 mg. I.V.	Ventricular tachycardia	Abolished	2
	200 mg. I.V.	Ventricular ectopic beats with or without bigeminy	Abolished	5
	400 mg. I.V.	Ventricular fibrillation	No effect	3
Procaine	10 cc. 1% in pericardial sac	Ventricular ectopic beats	Usually abolished	9
	10 cc. 1% in pericardial sac	Ventricular fibrillation	Possibly important in reversion to normal sinus rhythm*	1
Prostigmine	0.25 mg. I.V.	Tachycardia with sinus rhythm	Rate decrease averages 30 beats per minute	8
	0.25 mg. I.V.	Tachycardia with auricular fibrillation	Rate decrease averages 50 beats per minute	16
Atropine	0.1 mg. I.V.	Bradycardia with auricular fibrillation	Rate increase of 30 beats per minute	2
Adrenalin	5–10 cc. 1:1000 intracardiac	Cardiac arrest	None*	1
Calcium chloride (10%)	5–10 cc. intracardiac	Cardiac arrest	Bursts of ventricular ectopic beats	2

* See text for details of therapy in successfully reverted cases

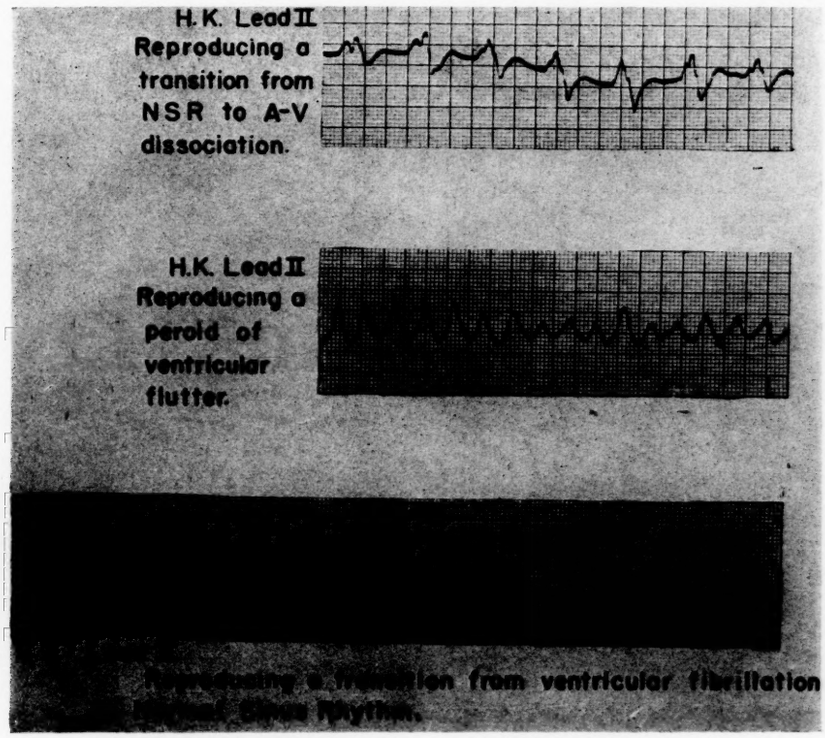

FIG. 2. Electrocardiogram showing wide range of arrhythmias noted in a patient during total operative procedure.

in the treatment of acute surgical arrhythmias. This information is presented in Table III.

Pronestyl was found very satisfactory for the abolition of ventricular ectopic beats and the cessation of ventricular tachycardia but failed to alter the course of ventricular fibrillation on three occasions. Procaine when injected into the pericardial sac in a 1 per cent solution often abolished ventricular ectopic beats and decreased myocardial irritability to manipulative procedures. In a single instance it may have been useful in causing the reversion of ventricular fibrillation to normal sinus rhythm when the heart surface was bathed with this solution.

Prostigmine proved to be a most useful tool for controlling all supraventricular tachycardias whether they occurred in sinus rhythm or in auricular fibrillation. There was a rate decrease of approximately 30 beats per minute in the former and 50 beats per minute in the latter, five to seven minutes after 0.25 mg. of the drug was given intravenously. Figures 3 and 4 present electrocardiographic evidence of the effect of prostigmine in the tachycardia of normal sinus rhythm and auricular fibrillation, respectively.

The parasympatholytic effect of atropine was utilized twice in treating bradycardia with auricular fibrillation. The patients received 0.1 mg. intravenously and a ventricular rate increase of 30 beats per minute resulted.

As previously noted, neither 1:1000 adrenalin nor 10 per cent calcium chloride injected into the myocardium was of any avail in cases of cardiac arrest although the latter did produce bursts of ventricular ectopic beats on two occasions.

COMMENTS

Incidence of Arrhythmias. Generally speaking, the incidence of serious arrhythmias producing a clinical effect was uncommon. Ventricular ectopic beats and auricular ectopic beats were present in twenty-four and nineteen patients, respectively, without significant alteration in the vital signs. Spontaneous cessation of auricular, nodal and ventricular ectopic beats was very common without any treatment.

Tachycardia was the next most common finding and its onset, prior to valvuloplasty, was in the majority of cases (fifteen of nineteen) associated with hypotension which required treatment. Experience with many patients with

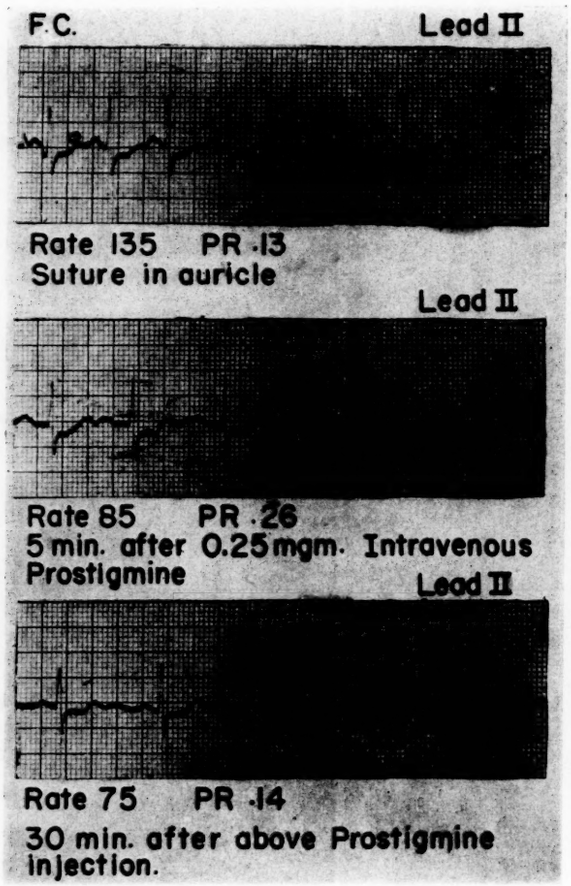

FIG. 3. Electrocardiogram showing slowing of tachycardia with normal sinus rhythm after intravenous prostigmine.

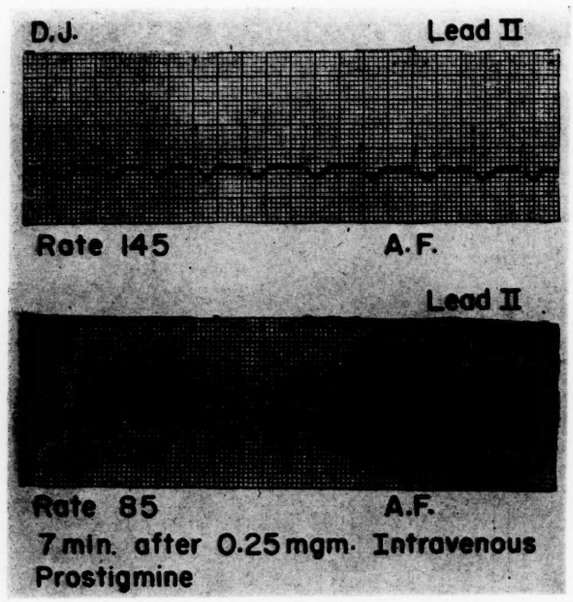

FIG. 4. Electrocardiogram showing slowing of tachycardia with auricular fibrillation after intravenous prostigmine.

severe mitral stenosis indicates that they are not well able to tolerate a rapid heart rate. In the presence of tachycardia the mitral patient must either accept a lowered cardiac output or raise his left auricular filling pressure (and hence his pulmonary vascular pressure).[9] The former adjustment may result in shock and the latter in pulmonary edema. Therefore, significant tachycardia in mitral stenosis dictates vigorous treatment.

The incidence of ventricular fibrillation (three of twenty-four cases or 13 per cent) was high, reflecting in part, at least, the fact that several of these patients were desperate operative risks. The reversion of ventricular fibrillation to normal sinus rhythm in one case is of note and very probably related to local bathing of the epicardium with one per cent procaine solution.

Operative Correlation with the Electrocardiogram. The relative stability of the electrocardiogram during cardiac surgery is noteworthy. Our findings confirm the earlier report of Harken and Zoll who remarked that minor conduction defects frequently associated with palpation, suturing or incision of the heart were well sustained and nearly as readily produced by extracardiac maneuvers, namely, endotracheal intubation, rib spreading, etc.[1]

It is interesting that pericardial incision, clamping of the auricle and auricular appendectomy produced no electrocardiographic alteration in over two-thirds of our series whereas the placing of auricular sutures caused ectopic auricular beats in nineteen and ventricular ectopic beats in two.

A review of the electrocardiograms taken while the surgeon's finger was palpating the heart revealed that palpation of the inner surface of the heart produces much more evidence of irritability than any other procedure evaluated except valvuloplasty itself. The finger in the auricle resulted in arrhythmias in all but nine of our cases, and palpation of the ventricular endocardium in all but two of the series. There were exactly double the number of patients with ventricular ectopic beats following palpation of ventricular endocardium as compared with those noted during contact with the ventricular epicardium.

Ventricular ectopic beats or ventricular tachycardia were observed in every case at the time of valve fracture, as might be anticipated from the foregoing observations. These abnormalities were usually transient and rarely required any specific treatment.

The duration of evidence of electrocardiographic abnormality after fracture of the valve varied from about five minutes to several hours but in every successful case there was a return to the preoperative pattern in that time.

Drugs. Pronestyl given in small dosage (0.2 to 0.4 gm.) intravenously in one to two minutes was found very efficacious in the treatment of ventricular ectopic beats and ventricular tachycardia as reported by many other authors.[10,11] It was successful in all such cases but was without effect in three cases of ventricular fibrillation although the dose was never large. No hypotensive effect from pronestyl was noted in anesthetized patients although such is commonly observed in unanesthetized patients.[9]

One per cent procaine solution in the pericardial sac was generally effective in the suppression of ventricular ectopic beats induced by manipulation of the heart.[2,7,12] The clinical impression exists that procaine epicardially may alter adversely the effective contraction of the myocardium.[13] We can express no opinion regarding this. Reference has already been made to the possible beneficial role of procaine solution in reverting a case of ventricular fibrillation to normal sinus rhythm.

A drug little reported in medical literature in reference to the treatment of cardiac arrhythmias is prostigmine methyl sulfate (supplied as 1:4000 solution for intravenous use).[14,15] We have used the drug quite extensively, and in this series on twenty-four occasions in fifteen patients. As pointed out earlier, tachycardia is poorly tolerated by patients with severe mitral stenosis, and in this group fifteen patients became hypotensive with their tachycardia. The average response in rapid auricular fibrillation was a drop in rate of 50 ventricular beats per minute (40 to 80) and in sinus tachycardia of 30 ventricular beats per minute (20 to 40) following the intravenous injection of 0.25 mg. of prostigmine.

There is a more marked response in digitalized as opposed to undigitalized patients. Response is usually maximum in five to ten minutes after an intravenous injection of the drug and is transient in duration, usually twenty to thirty minutes. The drug has proved useful in all supraventricular tachycardias due to its marked vagotonic effect, and no toxic effects of any sort have been noted in our experience.

Atropine sulfate in 0.1 mg. intravenous dosage was of help in the marked bradycardia seen in two patients with auricular fibrillation. It raised the ventricular rate approximately 30 beats per minute, presumably due to its lytic effect on vagus tone.[16]

Our experience with intracardiac adrenalin 1:1000 and also 10 per cent $CaCl_2$ solution in cardiac arrest does not warrant any conclusions except to point out that the latter may elicit ventricular ectopic beats where the former has failed to do so.[17]

SUMMARY

1. The electrocardiographic abnormalities witnessed during finger fracture mitral valvuloplasty have been presented and their correlation with operative procedures traced in twenty-four cases.

2. The indications, dosage and effect of some readily available drugs for the treatment of these arrhythmias have been discussed.

Acknowledgment: Dr. Dwight E. Harken performed the surgery together with his regular operating team and Dr. William Derrick administered the anesthesia. We are deeply indebted to them for their permission to quote the operating room experiences here reported and for their close cooperation and generous and patient help under circumstances which were often most trying. The authors wish to express their gratitude to Dr. Harold D. Levine, who gave so freely of his time and advice in interpreting the electrocardiograms, and to Dr. Arthur Bloomfield for his assistance in the preparation of this paper. The secretarial help of Miss Barbara Johnson and Miss Janice Young are hereby acknowledged.

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Modifications of the Pulmonary Circulation in Mitral Stenosis*

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CARDIAC catheterization and its accessory technics have been of great value in revealing the abnormal circulatory patterns of mitral stenosis.[1–3] Inability to measure the left atrial pressure in the intact patient, however, has limited understanding of these patterns. Without a method for measuring the left atrial pressure, for example, the physiologic consequences of pulmonary vascular changes commonly associated with mitral stenosis were not completely appreciated. The effect of these changes on increasing pulmonary arterial pressure, augmenting right ventricular work and altering osmotic relations across the pulmonary membrane are of considerable interest and are of particular importance in the pre- and post-operative evaluation of the patient undergoing mitral valve surgery.

Recently the pulmonary "capillary" pressure has been established as a reasonably reliable measurement of the pressure in the left atrium and pulmonary veins.[4–7] With this pressure and other data obtained at cardiac catheterization it is possible to determine the extent of pulmonary vascular changes in mitral stenosis and to differentiate between the effects of such changes and the effects attributable to stenosis of the mitral valve *per se* on the dynamics of blood flow through the lungs.[8–10] In addition the area of the mitral valve orifice can be estimated by the formula of Gorlin and Gorlin.[11]

It is the purpose of the present report to present data on the pressures and flow of blood through the lungs of twenty-two patients with mitral stenosis, with particular reference to the effects of left atrial pressure elevation and alterations in the pulmonary vascular bed. In addition these data are compared with and discussed in the light of two similar reports[8–10] that have recently become available in the literature.

SUBJECTS AND METHODS

Subjects. Twenty-two hospitalized patients with mitral stenosis of varying clinical severity were used in this study. All subjects had apical systolic murmurs in addition to diastolic murmurs but clinically the predominant lesion was mitral stenosis. Associated lesions of the other valves were not clinically apparent in any except one subject (D. R.) who had an associated tricuspid insufficiency. All patients were considered to be compensated at time of study; those with auricular fibrillation and a number of those with normal rhythm previously in failure had been maintained on digitalis. The majority of the patients were catheterized as part of routine pre-mitral commissurotomy evaluation and were moderately to severely restricted in activity by their heart disease.

Each subject was studied in the resting state five hours postabsorptive. A quick-acting barbiturate (usually sodium amytal 0.2 gm.) was administered one-half hour prior to the procedure.

Methods. Cardiac catheterization was performed in the usual manner. An inlying needle was inserted in the brachial artery. Pulmonary "capillary,"[4] pulmonary arterial and right ventricular pressures were recorded. Following re-positioning of the catheter in the pulmonary artery, expired air was collected and measured in a Tissot spirometer after three 3-minute flush-outs of the dead space in the collecting system. Mid-way during the collection of expired air samples of pulmonary and brachial arterial blood were obtained simultaneously.

* From the Cardio-Pulmonary Laboratory of the Departments of Radiology and Medicine of The New York Hospital—Cornell Medical Center, New York City, and from the National Heart Institute, Bethesda, Md. This investigation was supported by a grant from the New York Heart Association.

The catheter was then reinserted into the pulmonary "capillary" position and the patient made to exercise while recumbent by flexing and extending his legs in a bicycling manner at the rate of one cycle per two seconds for five minutes. During the last two minutes of the exercise pulmonary "capillary" and pulmonary arterial pressures were again recorded; expired air was collected in a previously evacuated Douglas bag and pulmonary and brachial arterial blood samples obtained. Pulmonary arterial pressure was measured each minute following exercise until it had returned to the resting level. The catheter was then withdrawn to the right atrium and pressure recorded.

Blood oxygen contents and capacities were determined by the Van Slyke-Neill manometric method.[12] Inspired and expired air samples were analyzed for carbon dioxide and oxygen with a 0.5 cc. Scholander micro-gas analyzer.[13] Oxygen consumption was calculated on the basis of the results of analysis of expired and inspired air for each individual according to the usual formula.[14]* All oxygen values were converted to STPD (0°c., 760 mm. Hg, dry). Pressures were measured with a Sanborn electromanometer and recorded simultaneously with a lead of the standard electrocardiogram by a direct writing Poly-viso recorder. Systolic and diastolic pressures were expressed as an average for several cardiac cycles and at least one respiratory cycle. Mean pressures were measured with the electromanometer by electronic integration. The zero reference point for all pressures was taken at 10 cm. anterior to the dorsal spine with the patient recumbent.

Cardiac output was calculated by the Fick principle. Pulmonary arteriolar resistance was determined by using the formula of Apéria:[15]

$$R_A = \frac{(PA_m - \text{"PC"}_m \times 1.332 \times 60}{CO}$$

Total pulmonary resistance was calculated similarly:

$$R_T = \frac{PA_m \times 1.332 \times 60}{CO}$$

The difference between these values was taken as the resistance provided by the stenotic mitral valve. The work of the right ventricle against pressure was calculated as follows:

$$W_{RV} = \frac{CO \times PA_m \times 13.6}{1000}$$

By substituting the $PA_m - \text{"PC"}_m$ gradient or "PC"_m for PA_m in the above formula this work could be apportioned between that expended in overcoming the pulmonary resistance and that used in overcoming mitral valvular resistance, respectively.

Following are the equivalents of the symbols in the above formulas:

R_A = pulmonary arteriolar resistance in dynes-sec.-cm.$^{-5}$.
R_T = total pulmonary resistance (arterioles + mitral valve) in dynes-sec.-cm.$^{-5}$.
PA_m = *mean* pulmonary arterial pressure in mm. Hg.
"PC"_m = *mean* pulmonary "capillary" pressure in mm. Hg.
CO = cardiac output in L./min.
W_{RV} = work of right ventricle against pressure in kg.M./min.

RESULTS

Cardiac Output. The average resting cardiac output per square meter of body surface area (cardiac index) was significantly lower than normal and ranged from 1.47 to 3.57 L./min./M^2. In six subjects the output was within normal limits. (Table I.)

The response of cardiac output to exercise was distinctly limited, an increase in cardiac index of 0.8 to 1.0 L./min./M^2 normally being expected. Only four of the six subjects whose resting outputs were normal were able to respond normally to exercise. Three others with subnormal resting outputs were able to effect appropriate increases in output but their exercise indices did not attain the expected level. Cardiac output decreased during exercise in four additional subjects despite an average increase in oxygen consumption of 77 cc./min./M^2.

The arteriovenous oxygen differences were large at rest and particularly large during exercise, reflecting the increased tissue extraction of oxygen from the blood occasioned by the inadequate peripheral blood flow. (Table I.)

* The respiratory exchange ratios (R.Q.) of these subjects were too variable, particularly during exercise, to permit the use of mean correction factors for adjusting expired to inspired air volume. The use of proposed correction factors of 1.007 at rest and 1.01 during exercise[8,9] introduced an error of −14 per cent in the resting oxygen consumption of one subject and a +15 per cent error in the exercise oxygen consumption of another patient in this series. The resulting errors in cardiac output were of the same magnitude.

Pulmonary "Capillary" and Arterial Pressures. The mean pulmonary venous pressure as measured from the pulmonary "capillary" position averaged 28 mm. Hg, two to three times the normal value of 9 mm. Hg at rest. A remarkable grouping of pulmonary "capillary" pressures about the 25 to 30 mm. Hg range (i.e., plasma osmotic pressure levels) was noted; in only two subjects did the pressure exceed this limit significantly at rest. During exercise the mean pulmonary "capillary" pressure rose abruptly in all subjects regardless of the degree of change of pulmonary blood flow. In one subject the pressure attained the strikingly elevated level of 55 mm. Hg. (Table II.) Despite elevations of pulmonary "capillary" pressure above plasma osmotic levels for periods of two minutes or more during exercise, overt signs of pulmonary edema did not develop.

As previously observed[7,8] the contours of the pulmonary "capillary" pressure tracings were at times helpful in distinguishing between pure stenosis of the mitral valve and stenosis complicated by insufficiency. (Figs. 1 and 2.) On other occasions the tracings were so artifactual as to be valueless for this purpose.

Pulmonary arterial hypertension, greatly aggravated by exercise, was present in all subjects. The average mean pulmonary arterial pressure was slightly more than three times normal at rest and almost five times normal during exercise. Following exercise the pressures did not return to resting levels for periods of two to ten minutes. Three subjects had resting pulmonary arterial pressures in the range of normal systemic blood pressure; five others attained such elevated levels during exercise. (Table II.)

Pulmonary Arteriolar Resistance. In only three patients was the elevation of pulmonary arterial pressure wholly related to the increased pulmonary "capillary" pressure, the PA-PC pressure

TABLE I

PHYSICAL CHARACTERISTICS, CARDIAC RHYTHM, MITRAL VALVE AREA AND CARDIAC OUTPUT DATA DURING REST AND EXERCISE IN MITRAL STENOSIS

Patient	Age, Sex	Body Surface Area (M^2)	Cardiac Rhythm	Mitral Valve Area ($cm.^2$)	Oxygen Consumption (cc./min./M^2)		Arteriovenous O_2 Difference (vol. %)		Cardiac Index (L./min./M^2)	
					Rest	Exercise	Rest	Exercise	Rest	Exercise
J. C.	26, M	1.75	NR	2.68	183	361	5.2	7.4	3.53	4.88
F. G.	22, M	1.66	NR	....	189	428	5.5	10.0	3.44	4.28
A. D.	45, M	1.60	NR	....	146	378	4.7	9.4	3.10	4.03
M. B.	21, F	1.58	NR	1.32	139	268	4.1	7.2	3.40	3.72
J. Mc.	24, M	1.80	NR	1.82	146	352	4.8	7.2	3.03	4.86
M. O.	36, F	1.57	NR	2.17	139	296	3.9	8.0	3.57	3.68
B. S.	22, F	1.57	NR	1.19	125	287	5.3	7.4	2.36	3.87
J. G.	40, M	1.83	AF	....	170	399	6.9	11.3	2.47	3.54
N. L.*	22, F	1.35	AF	0.64	146	234	6.1	8.2	2.39	2.85
M. F.*	32, F	1.47	AF	0.64	132	237	6.6	9.4	2.00	2.52
A. Y.*	29, F	1.84	AF	1.37	148	305	6.4	12.1	2.31	2.52
J. M.	41, M	1.73	AF	1.27	135	212	6.1	9.3	2.22	2.28
V. M.*	45, F	1.53	AF	0.70	126	220	5.1	9.0	2.47	2.44
M. L.*	29, F	1.44	AF	1.18	177	260	6.8	11.2	2.58	2.32
D. R.*	45, F	1.48	AF	0.90	150	180	6.5	8.2	2.31	2.20
R. H.	37, F	1.58	AF	0.62	156	269	8.3	12.2	1.87	2.20
K. M.*	46, F	1.50	AF	0.73	115	238	5.7	10.4	2.03	2.29
P. B.	39, M	1.69	AF	0.68	122	350	6.7	12.5	1.82	2.80
G. W.	24, F	1.56	NR	1.27	126	226	5.6	10.5	2.26	2.15
E. J.	31, F	1.60	NR	1.21	121	241	6.3	12.3	1.91	1.96
J. D.	24, F	1.48	NR	0.94	146	...	8.1	....	1.80	....
G. N.*	34, F	1.33	AF	0.92	156	270	10.6	13.3	1.47	2.03
Average	32	1.59	...	1.16	145	286	6.1	9.8	2.47	3.02

* Patients with associated tricuspid insufficiency.

gradient and pulmonary arteriolar resistances being essentially normal. In the remaining subjects increased pulmonary arteriolar resistances were observed and were consequently associated with pulmonary arterial pressures elevated out of proportion to the pulmonary "capillary" pressures.

Pulmonary arteriolar resistances (Table II) varied widely and without relationship to the mitral valve area or the pulmonary "capillary" pressures although such relationships have been observed previously.[16] For example: there was no increase in resistance (135 dynes-sec.-cm.$^{-5}$) in a patient with a pulmonary "capillary"

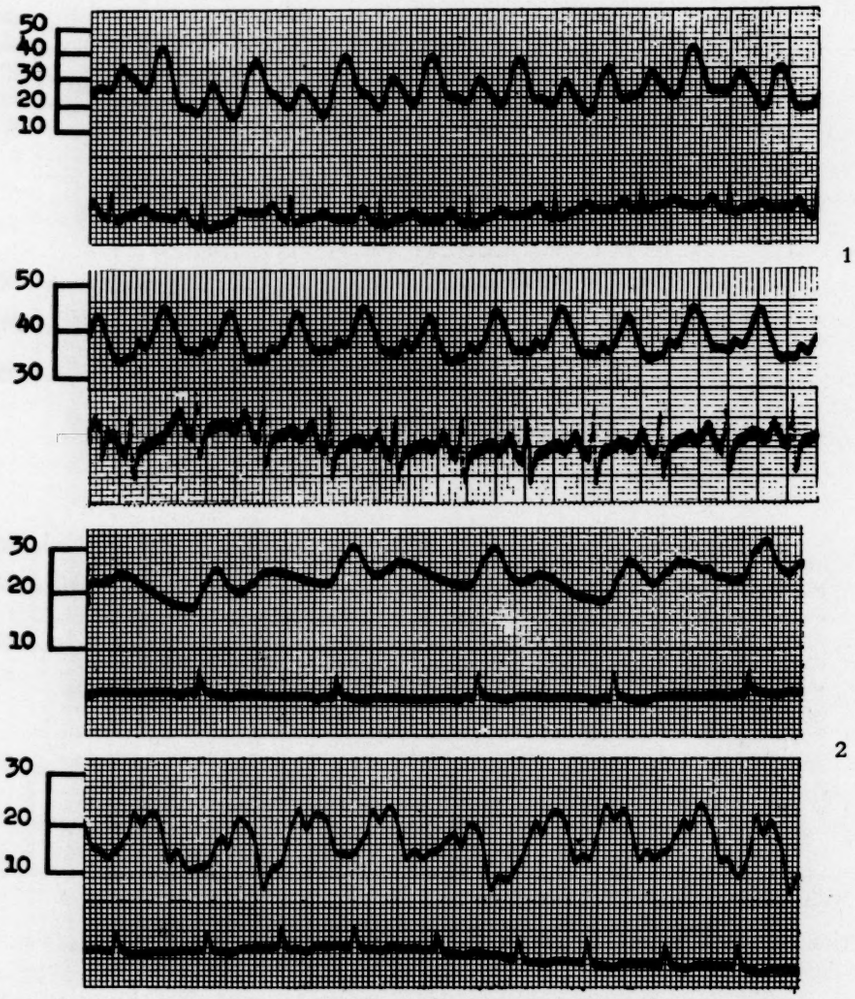

FIG. 1. *Upper strip:* Pulmonary "capillary" pressure and simultaneously recorded EKG from a patient with mitral stenosis and insufficiency (J. Mc.). *Lower strip:* Left atrial pressure recorded at time of mitral commissurotomy from same patient. The largest pressure peak in both tracings occurs well after the QRS complex and represents regurgitation due to insufficiency of the mitral valve. The smaller wave beginning prior to the QRS in the pulmonary "capillary" tracing represents left atrial contraction reflected back through the pulmonary veins. The greater mean pressure in the left atrium is probably due to altered hemodynamics in the open thorax.

FIG. 2. *Upper strip:* Pulmonary "capillary" pressure curve from patient (B. S.) with "pure" mitral stenosis showing large left atrial contraction wave reflected through the pulmonary veins and no evidence of regurgitation. *Lower strip:* Right atrial pressure curve (patient A. Y.) showing no atrial contraction (auricular fibrillation) and a large typical peak-plateau pressure rise occurring after the QRS due to tricuspid insufficiency.

pressure of 36 mm. Hg, and a markedly elevated resistance (2049 dynes-sec.-cm.$^{-5}$, a value twice the normal systemic arteriolar resistance) was present in a subject with a "capillary" pressure of 25 mm. Hg.

A definite inverse correlation ($r = -0.724 \pm 0.106$; $p = <.01$) between resting cardiac output and the *total* pulmonary resistance (vascular plus valvular resistances) was noted. Expressed in a log-log manner the correlation was highly significant ($r = -0.874 \pm 0.053$; $p = <.01$) and described a straight line. (Fig. 3.)

Work of the Right Ventricle. Because of pulmonary arterial hypertension the work of the right ventricle against pressure was increased in all subjects, including those with small cardiac outputs. The average values were twice normal at rest and three times normal during exercise. (Table II.) Work performed in overcoming the resistance of the pulmonary vessels was greater than normal, except in the three patients with normal arteriolar resistance. In four instances more work was expended in propelling blood through the resistant pulmonary vessels than through the stenotic mitral valve. (Fig. 4.)

Mitral Valve Area. The calculated mitral valve orifice areas ranged from 0.62 to 2.68 sq. cm. in contrast to the normal of 4–6 sq. cm. (Table I.) In our experience the calculated areas have checked within 0.2–0.4 sq. cm. with those estimated at autopsy or by the surgeon at time of mitral commissurotomy. Because of the invariably irregular orifice of the stenotic mitral

TABLE II

LESSER CIRCUIT PRESSURES, ARTERIOLAR RESISTANCE AND RIGHT VENTRICULAR WORK DURING REST AND EXERCISE IN MITRAL STENOSIS

Patient	Pulmonary Artery Pressure (mm. Hg)				Mean Pulmonary "Capillary" Pressure (mm. Hg)		Resting Right Ventricular Diastolic Pressure (mm. Hg)	Resting Mean Right Atrial Pressure (mm. Hg)	Pulmonary Arteriolar Resistance (dynes-sec.-cm^{-5})		Total Pulmonary Resistance (dynes-sec.-cm^{-5})		Right Ventricular Work (kg.M./min./M^2)	
	Rest		Exercise											
	S/D	M	S/D	M	Rest	Exercise			Rest	Exercise	Rest	Exercise	Rest	Exercise
J. C.	30/12	20	50/28	38	13	26	4	4	91	112	259	356	0.96	2.52
F. G.	61/33	46	108/64	82	33	..	10	9	182	....	644	922	2.15	4.78
A. D.	69/30	48	105/43	71	..	..	3	−0.5	....	....	764	870	2.03	3.89
J. Mc.	60/30	45	118/60	84	28	46	10	7	249	347	659	768	1.86	5.55
M. B.	49/30	37	82/50	57	25	44	4	−2	179	177	551	598	1.70	2.88
M. O.	65/26	46	80/46	59	29	40	8	4	242	263	655	816	2.24	2.95
B. S.	61/29	39	97/42	68	29	45	8	3	216	302	842	897	1.25	3.58
J. G.	59/24	47	134/75	98	29	..	9	8	318	....	831	1201	1.58	4.71
N. L.*	44/24	36	70/39	52	27	42	7	9	223	208	891	1079	1.17	2.00
M. F.*	66/28	42	84/32	50	28	35	10	12	326	324	1142	1080	1.14	1.71
A. Y.*	52/26	36	76/35	50	29	44	12	16	132	103	677	861	1.13	1.71
J. M.	54/27	37	70/45	56	24	40	6	7	271	324	770	1133	1.12	1.74
V. M.*	57/24	35	76/39	54	26	34	3	4	190	429	740	1157	1.18	1.79
M. L.*	56/30	38	74/44	53	30	40	7	11	172	311	816	1268	1.34	1.67
D. R.*	66/31	46	76/34	53	28	..	6	14	421	....	1074	1299	1.45	1.59
R. H.	59/31	41	84/43	56	36	..	7	5	135	....	1107	1286	1.04	1.68
K. M.*	56/29	44	106/52	69	29	55	7	7	394	326	1157	1608	1.21	2.15
P. B.	66/37	47	140/78	100	31	..	4	7	417	....	1224	1686	1.16	3.81
G. W.	99/41	63	157/51	92	29	40	11	10	772	1237	1430	2188	1.93	2.69
E. J.	107/56	75	110/64	84	29	37	9	7	1201	1200	1959	2145	1.95	2.23
J. D.	155/73	97	170/85	118	28	..	20	18	2065	....	2903	....	2.38	....
G. N.*	107/61	75	127/86	101	25	35	8	8	2049	1954	3074	2990	1.50	2.79
Average	68/33	47	100/52	70	28	40	8	8	448	508	1099	1248	1.52	2.78

S/D = systolic/diastolic; M = mean

* Patients with associated tricuspid insufficiency.

valve precise measurement of its area at autopsy is difficult, and quantitative estimates based on the finger touch impression of the surgeon are subject to greater inaccuracy. Close agreement between the calculated area and the measured area is therefore not to be expected.

pulmonary "capillary" pressure influenced by left atrial pressure elevation due to regurgitation from the ventricle during *systole*, and the less is it representative of the pressure required to fill the left ventricle during *diastole*. The formula for calculation of the mitral valve area is therefore

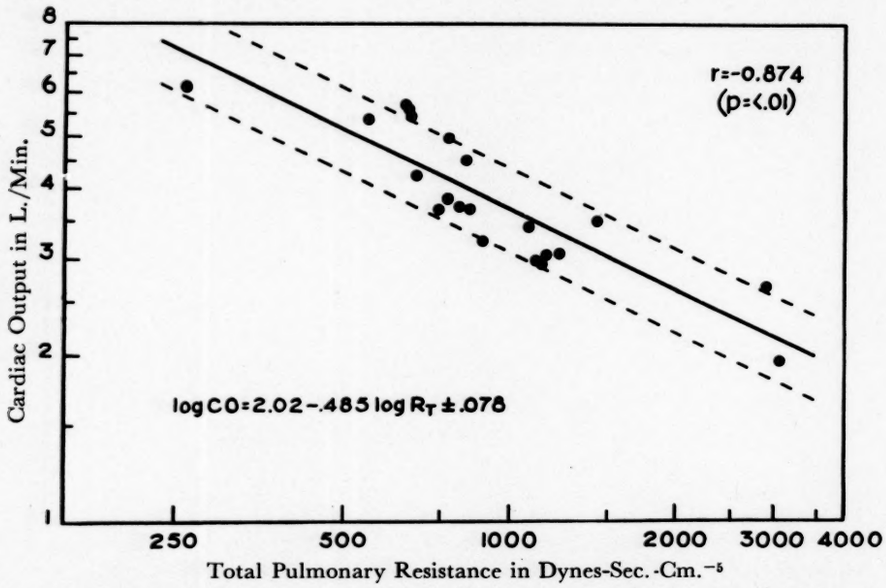

FIG. 3. Relationship between cardiac output and total pulmonary resistance in mitral stenosis. Both variables were plotted on logarithmic coordinates. The equation for the straight line is given in the lower left. Dotted lines represent standard deviation of the equation.

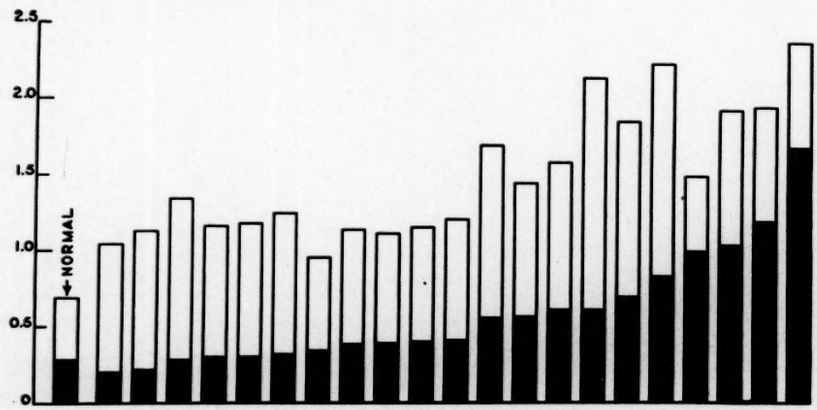

FIG. 4. Work of the right ventricle in mitral stenosis in twenty-one patients in whom required data were obtained. Total work in dynes-sec.-cm.$^{-5}$ per square meter body surface area for each subject is represented by an entire vertical column. The height of the black area represents the pressure-work done in propelling blood through the pulmonary arterioles; the remaining white area, work performed against the mitral valve.

The calculated mitral valve area is a valuable physiologic measurement in cases not complicated by appreciable mitral insufficiency. The greater the mitral insufficiency, the more is mean

neither theoretically nor actually applicable in patients with degrees of insufficiency large enough to influence the pulmonary "capillary" pressure significantly.

Correlation of a high degree ($r = 0.898 \pm 0.046$; $p = < .01$) was present between the resting cardiac output and the mitral valve area. (Fig. 5.) The closeness of this correlation reflects the relative similarity of the pulmonary "capillary" pressures among the patients. For a given

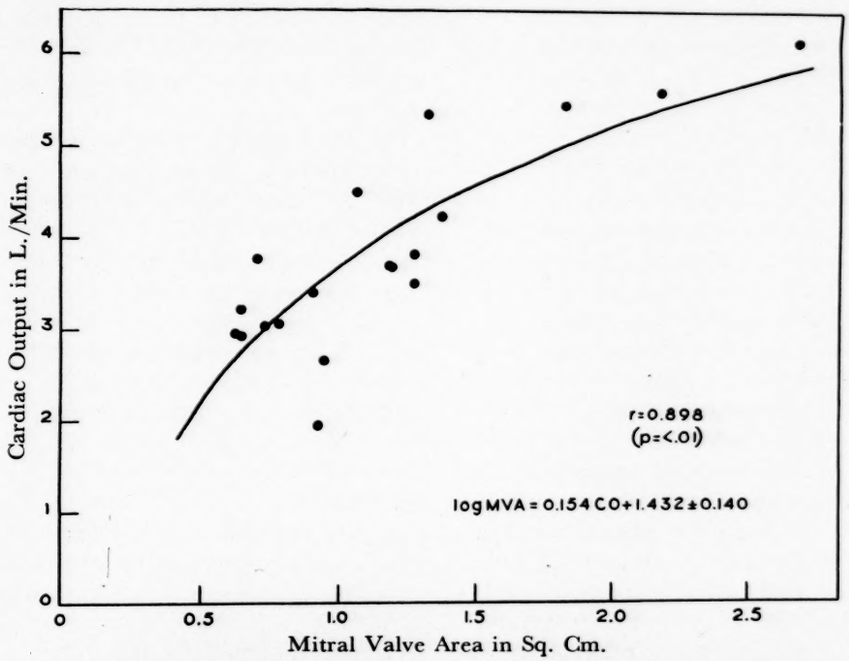

FIG. 5. Relationship between cardiac output and calculated area of the mitral valve orifice. Knowing the cardiac output, the mitral area may be predicted from the equation describing the curve.

left atrial pressure, the wider the mitral orifice, the greater the rate of blood flow through it. On the basis of this relationship it is possible to predict the area of the mitral valve if the resting cardiac output is known. The accuracy of the prediction is augmented if the pulmonary "capillary" pressure is 25 to 30 mm. Hg. A normal cardiac index was observed with a mitral valve area as low as 1.32 sq. cm. although in this subject blood flow during exercise was limited. In subjects with normal resting and exercise cardiac indices mitral valve areas exceeded 1.82 sq. cm.

Incidence of Tricuspid Insufficiency. An interesting finding was the presence of the typical pattern of tricuspid insufficiency in the right atrial pressure tracings of eight (36 per cent) subjects. All had auricular fibrillation. The typical configuration of the right atrial pressure curve in tricuspid insufficiency has been described previously[17] and an example from this series is shown in Figure 2. In only one of the subjects had tricuspid insufficiency been diagnosed clinically.

Associated tricuspid stenosis was not present. The fact that right atrial *mean* pressures in these patients exceeded the right ventricular diastolic pressures reflected the rise in right atrial pressure occurring during right ventricular *systole* because of the valvular insufficiency. (Fig. 2.) In no instance was there a significant difference between the right atrial and right ventricular pressures during ventricular *diastole* as would occur with stenosis of the valve.

The mean increase in cardiac index of 0.20 ± 0.31 L./min./M² during exercise in the eight patients with complicating tricuspid insufficiency was significantly less than the 0.79 ± 0.59 increase in those without this valvular lesion ($p = 0.01$). The pulmonary hemodynamics of the two groups were otherwise essentially similar. Tricuspid insufficiency was associated with greatly elevated mean right atrial pressures, as high as 16 mm. Hg, and large right atria as outlined by the cardiac catheter.

Because of the high incidence of tricuspid insufficiency right atrial pressure could not be used as an index of the filling pressure of the

right ventricle. The average right ventricular end-diastolic pressure, the true filling pressure, was increased above normal reflecting thereby the increased work burden of the right ventricle.[18]

COMMENTS

Stenosis of the mitral valve imposes a number of modifications on the pulmonary circulation. In order to maintain filling of the left ventricle through the stenotic valve, left atrial pressure is increased to two or three times normal and accordingly a similar increment in the pressure of the pulmonary veins occurs. In the face of pulmonary venous pressures twice as large as normal pulmonary arterial pressure, the pulmonary arterial pressure rises to preserve the gradient needed to facilitate flow through the arterioles and capillaries of the lungs. The resistance of the pulmonary arteriolar bed, normally very slight, may remain normal but in the majority of patients with mitral stenosis it is increased. Arteriolar resistance is so markedly abnormal in some subjects that more work is performed in pushing blood through the pulmonary vessels than through the stenotic valve. With alterations in the pulmonary vascular bed, pulmonary arterial pressure is increased out of proportion to the rise in pulmonary venous pressure and may attain values equivalent to systemic arterial pressure.

The burden of effecting such wide changes in pressure relationships within the lesser circuit falls directly upon the right ventricle. The diastolic pressure increases in accordance with the classical principles of myocardial behavior[19–21] as the work of the right ventricle at rest is doubled or more. The amount of blood the ventricle ejects against the increased pressure is normal in some patients; but as the total resistance to flow increases or as the mitral valve orifice narrows, the cardiac output at rest declines in a mathematically predictable fashion.

With the need for augmentation of cardiac output during exercise, further increases in pulmonary venous and arterial pressures occur in mitral stenosis. Under these circumstances the right ventricle performs more work against pressure, but usually it is only capable of effecting increments in output that are small in proportion to the degree of exercise performed. In some patients exercise is accompanied by a fall in cardiac output.

A decrease in cardiac output during exercise in mitral stenotics has been observed previously.[10] This paradoxical response in four of the patients in the present series may be attributed to one or more factors: (1) the right ventricle was so taxed at rest that further demands placed on it resulted in decrease in output in accordance with the Starling principle; (2) the failure of the patients to reach a steady state during exercise, the Fick principle being applicable only to the steady state; (3) the presence of complicating tricuspid insufficiency in three of the subjects.

In the series reported by Draper and associates thirteen of twenty-five patients with mitral valvular disease exhibited decreases in cardiac output during exercise.[10] The very high ventricular diastolic and greatly oscillating right atrial pressures in their patients suggest right ventricular incompetency of a greater degree or a higher incidence of tricuspid disease than manifested by the subjects in the present report. Also the duration and degree of exercise (judging by the average increase in oxygen consumption of 34 cc./min./M^2 during exercise in their patients with a paradoxical fall in cardiac output) was less than that in this study. The oxygen consumption of two of their patients fell during exercise, a finding not readily explained.

The 36 per cent incidence of clinically undetected tricuspid insufficiency in the present group of mitral stenotics is comparable to the incidence in autopsy studies on patients with mitral stenosis.[22,23] Whether tricuspid insufficiency was the result of previous rheumatic valvulitis or the result of widening of the valve ring secondary to right ventricular and atrial dilatation cannot be determined. It is significant that with improvement following mitral commissurotomy evidence of tricuspid insufficiency, previously so clear-cut in the right atrial pressure tracing of one of the patients (G. N.), disappeared. In another patient (K. M.) despite improvement in blood flow and pressures after commissurotomy, tricuspid insufficiency persisted. (Table III.)

Pathologic studies reveal that arteriosclerotic changes in the lungs frequently accompany mitral stenosis.[24,25] In addition to these anatomic alterations there are *physiologic* factors that increase the resistance of the pulmonary arterioles to blood flow. Thus remarkable decreases in resistance may accompany the improvement accruing from surgical widening of the mitral valve.[9,10] (Table III.) The pathogenesis of neither anatomic nor physiologic changes is clearly

understood. The degree to which they are reversible is of great importance in determining the success of mitral valve surgery since a considerable portion of the increased work of the right ventricle is expended on driving blood through the altered pulmonary vessels. Indeed in some instances more work is done against the pulmonary vessels than against the stenotic mitral valve.

gave histories of having had acute episodes of pulmonary edema. During catheterization, however, definite evidence of pulmonary edema was not noted in any of the subjects, despite average pulmonary "capillary" pressures of 28 mm. Hg at rest and 40 mm. Hg for at least two minutes during exercise. In the series of Gorlin and coworkers[8] pulmonary edema at rest was noted only in those mitral stenotics with pulmonary "capillary" pressures averaging 40 mm. Hg (a value considerably above colloid osmotic pressure); whereas in those without pulmonary edema at rest, the pressure averaged 24 mm. Hg. Apparently changes in the alveolocapillary membrane[23] resulting in decreased permeability to fluid or increased pericapillary tissue pressure hinder the emergence of fluid into the alveoli. Prolonged elevations of pulmonary "capillary" pressure well in excess of plasma colloid osmotic levels are therefore required prior to the occurrence of clinically significant pulmonary edema in the usual patient with mitral stenosis.

TABLE III

PHYSIOLOGIC DATA ON THREE PATIENTS WITH MITRAL STENOSIS BEFORE AND AFTER MITRAL COMMISSUROTOMY

Patient	Operation	Cardiac Index (L./min./M²)		Pulmonary Artery Pressure (mm. Hg)				Mean Pulmonary "Capillary" Pressure (mm. Hg)		Pulmonary Arteriolar Resistance (dynes-sec.-cm.⁻⁵)		Mean Right Atrial (mm. Hg)	Mitral Valve Area (cm.²)
		Rest	Exercise	Rest		Exercise		Rest	Exercise	Rest	Exercise		
				S/D	M	S/D	M						
G. N.	Before	1.47	2.03	107/61	75	127/86	101	25	35	2049	1954	8 (TI)	0.92
	After	2.72	3.51	105/44	58	136/57	83	20	..	828	....	2	1.28
K. M.	Before	2.03	2.29	56/29	44	106/52	69	29	55	394	326	7 (TI)	0.73
	After	2.53	2.83	47/24	32	80/33	53	18	38	293	261	7 (TI)	1.35
G. W.	Before	2.26	2.15	99/41	63	157/51	92	29	40	772	1237	10	1.27
	After	3.56	3.73	54/24	37	96/36	63	13	20	341	583	6	2.67

It has been argued that the arteriolar resistance serves to protect the pulmonary capillaries from increases in cardiac output too large to bypass the stenotic mitral valve without large increases in pulmonary "capillary" pressure.[16] That such a protective mechanism falls short of the mark is indicated by the comparable elevations of pulmonary "capillary" pressures during rest and exercise regardless of the degree of arteriolar resistance. The increased resistance appears to serve little useful purpose and with regard to the right ventricle is, as Hamilton has noted, " . . . like putting your foot on the brake while accelerating."[26]

Experimentally, pulmonary edema occurs when the pulmonary venous and pulmonary capillary pressures approach levels in the range of the colloid osmotic pressure of the plasma (i.e., 25 to 30 mm. Hg).[27,28] It is therefore not surprising that many of the subjects in this report

SUMMARY

As a result of the mechanical effect of the narrowed mitral orifice, circulation through the lungs is greatly modified in mitral stenosis. Hypertension in all segments of the pulmonary vascular bed—venous, capillary and arterial—

develops as the consequence of the invariably present elevation of left atrial pressure. The cardiac output is reduced and relatively fixed. The flow resistance of the pulmonary arterioles is increased, sometimes markedly, causing an elevation of the pulmonary arterial pressure out of proportion to the pulmonary venous pressure and thereby accounting for a considerable portion of the increased pressure-work load of the right ventricle. The decrease in resistance after mitral commissurotomy suggests that physiologic, as well as previously described anatomic factors, are responsible for the arteriolar resistance. The hydrostatic pressure in the pulmonary capillaries is frequently equal to plasma colloid osmotic pressure and exceeds it during brief periods of exercise without development of frank pulmonary edema. This suggests that alterations in the alveolocapillary membrane tending to prevent the formation of pulmonary edema are present in mitral stenosis. Tricuspid insufficiency without physiologic stenosis is found in approximately one-third of patients with mitral stenosis.

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Slit-Kymographic Evidence that Nitroglycerine Decreases Heart Volume and Stroke Volume*

While Increasing the Amplitude of Ballistocardiographic Waves

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During the past eighty years no drug has proved superior to nitroglycerine in warding off or cutting short attacks of angina pectoris. Early students were impressed by the flush, palpitation and tachycardia which it evokes, as indirect evidences of increased cardiac activity. Its action on angina was therefore ascribed solely to coronary vasodilatation, and its use was largely confined to this disease. However, in 1915, Lindhard and Jarisch[1] reported that although amyl nitrite raised the pulse rate and minute flow of blood, the mean stroke volume, calculated by the nitrous oxide uptake method, fell 32 per cent in ten trials on five subjects. In 1925 Holman and Beck[2] reported a striking decrease in the cardiac area of roentgenograms in dogs given amyl nitrite. This persisted after the initial drop in arterial pressure had disappeared. In 1933 Weiss and Ellis,[3] using Bock's technic for measuring cardiac output by the Fick principle, observed that sodium nitrite decreased stroke volume on the average of 15.5 per cent in ten subjects; minute volume rose or fell slightly. In 1937 Weiss, Wilkins and Haynes[4] produced evidence that nitrites had a striking effect in diminishing the tone of the venous reservoir. It decreased return flow to the heart greatly when subjects were upright but had little effect when they were recumbent.

Nearly all observers have found insignificant changes in arterial pressure when recumbent normotensive subjects were given any of the nitrites; in the upright posture diastolic pressure is well maintained but systolic pressure may fall as venous pressure and stroke volume diminish.[4] However, the pounding pulse, dilated temporal arteries and warm skin have convinced most students that the larger arteries and the venules are relaxed, even though arteriolar resistance is well maintained. In a single experiment 0.4 mg. of nitroglycerine more than doubled the velocity of body motion due to the heart beat. This occurred in an erect subject and was reported in 1922 by Heald and Tucker.[5] Recent studies made with a low frequency ballistocardiograph led to the report that in ten subjects this drug caused a mean increase of 27 per cent in stroke volume.[6] In one subject left ventricular work per minute appeared to have increased over 100 per cent. As no fall in arterial pressure was noted, the observers concluded that nitrites increased cardiac work per beat.

Since previous studies on nitrites indicated a decreased stroke volume, rather than the increase deduced from the ballistocardiograms, we have made further observations on this problem. It seemed especially desirable to follow the size of the heart since it is generally agreed that cardiac volume parallels cardiac work and oxygen use per beat. The possibility existed that nitroglycerine (glycerol trinitrate), being a nitrate, had a different action than sodium or amyl nitrite. There was also a strong probability that the ballistocardiogram yielded fallacious results in estimating drug action on stroke

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volume. Since most anginal patients take the drug while erect, studies were made in the upright as well as the recumbent posture.

METHODS

Using the standard slit kymograph with slits 12 mm. apart we recorded the cardiac antero-posterior roentgen silhouette in six subjects in the erect position, before and six minutes after putting 0.6 mg. of fresh nitroglycerine under the tongue. Method A of Keys et al.[7] was used for calculating volume and stroke from these films. Using a special kymograph for recumbent subjects, similar films with synchronous ballisto-cardiograms were recorded in four subjects before and six minutes after nitroglycerine; and in one subject two control films as well as five and eight minute films were made. The ballisto-cardiograms were made directly, with a displacement type electromagnetic pick-up on the shins, and were recorded simultaneously on the x-ray film and on a direct-writing galvanometer. The sensitivity was 1 mv. deflection for a displacing force of 125 to 150 gm. in 70 kg. subjects.

On another occasion subjects used in tests with the slit kymograph were studied before and three, five, eight and ten minutes after nitroglycerine with the same displacement ballistocardiograph and simultaneously with an electromagnetic velocity ballistocardiograph. The displacement pick-up has its output integrated by a 20 mfd. condenser across the leads;[8] the velocity pick-up used no filter or one of 2 mfd. which caused no significant integration. The velocity ballistocardiograph is accurately calibrated by mounting the magnet on a pendulum. This swings in the beam of light from a galvanometer which records the induced voltage. The sensitivity of this pick-up was such that motion of the magnet relative to the coils gave 1 mv. for a velocity of 0.24 mm./second. The peak of a wave of velocity precedes that of displacement by one-fourth of a cycle, as is expected with a velocity curve and its first integration, the displacement curve. The displacement curves are essentially identical with those inscribed by Starr's high frequency table.[9]

The tests of recumbent subjects were made after half an hour's rest on the table under basal conditions. The tests of erect subjects were made by interrupting them in their usual activities in order to simulate the anginal situation. These subjects walked slowly about the room before and after taking the drug and were motionless for only ten to fifteen seconds before taking a roentgenogram. In taking the films the subjects tried to hold their breaths in the same phase of respiration each time; this was checked by the position of the diaphragm on the films. Ballisto-cardiograms in the last series were recorded with normal breathing and with breath held in mid-position. Exact distances of the x-ray tube from the heart and the film were not measured, but target-film distance was 36 inches in all studies of erect subjects, 38 inches with the recumbent subjects. Distance from sternum to film was less than 1 inch when erect, nearly 2 inches when recumbent. The calculated cardiac volumes were not corrected for the magnification by the divergent beam since percentage changes rather than absolute values were sought. In making the outlines of the systolic and diastolic volumes we modified Keys' method[7] as follows: The left borders were traced carefully and the upper, lower and right borders, drawn on the control film according to Keys' method A, were copied on the postnitroglycerine tracings. Lead strips and crosses taped to the subjects chests made centering accurate (Fig. 1), and the possibility of exaggerating the drug effects on ventricular volume and stroke volume were minimized by this method. The change in right border reflects change in venous pressure and auricular filling rather than in volume of the ventricles. Stroke volumes are lower than with Keys' original method. The percentage of change, both in volume and in stroke, is less than when right border motion is included. The kymographic method, although not dependable for absolute values from subject to subject, seems valid for variations in heart volume and, with a higher degree of error, for variations in stroke volume in the same subject.

RESULTS

The tachycardia observed in fifteen of seventeen experiments in normal subjects, and in two experiments in a patient with angina, apparently has some relation to apprehension and reaction to the flush and palpitation. One subject who took part in all three series had a rise in rate from 66 to 105 in the first test while recumbent (Table I, D), and a fall from 100 to 92 in the second test (Table II, D) made while erect after walking about. In the third test (Table III, D) his rate rose from 61 to 74 while recumbent. Several days intervened between duplicate tests. The mean rise in rate was 22 per

cent in the first series (recumbent), 19.5 per cent in second series (erect), but only 11.6 per cent in the third series (recumbent). The subjects of the third series were all familiar with the action of the drug; in the first series all were taking it for the first time. Cardiac acceleration is the most marked and consistent change we observed in any function measured. It apparently is less with sodium nitrite,[3,4] than with nitroglycerine, in the usual doses. With amyl nitrite this action is even more marked.[1]

Decrease in heart size (Figs. 1–4) occurred in each of eleven experiments. (Tables I and II.) The mean change in diastolic volume was −9 per cent in recumbent subjects and −13 per cent in erect subjects. Decrease in stroke volume occurred in five of six erect subjects, the mean change being −11 per cent. (Table II.) In recumbent subjects (Table I) the mean stroke volume decreased 6 per cent, with a rise in only one of five subjects. The stroke volumes, representing differences between systolic and diastolic volumes, naturally are subject to considerable error. Yet we may conclude from these data that there usually is a decrease in stroke volume after nitroglycerine, similar to that observed by others with more precise methods in tests of amyl nitrite[1] and sodium nitrite.[3] This change is greater in the upright than in the recumbent position, as was suggested by studies

TABLE I

CONTROL VALUES AND PERCENTAGE CHANGES AFTER NITROGLYCERINE IN RECUMBENT NORMAL SUBJECTS*

Subject	Diastolic Volume Control (ml.)	Change at 6 min. (%)	Stroke Volume Control (ml.)	Change at 6 min. (%)	Heart Rate Control (Beats/min.)	Change (%)	Minute Volume Control (ml./min.)	Change (%)	Amplitude of I-J Wave Control (mv.)		Change (%)
Normals											
Kp	908	- 6	52	-10	68	+14	3540	+ 3	1.3		+33
Z	871	-11	43	-15	71	+ 1	3300	- 8	2.9		+ 8
C	1,024	- 6.5	34	-13	78	+25	2340	+ 8	23.5	2.4	+ 6
S	744	-14	37	+ 8	54	+26	2000	+35	14.7	1.5	- 6
D	848	- 7	45	- 1	66	+44	3060	+30	1.6		-19
Mean or average	875	- 8.9	42	- 6.2	67	+22	2848	+13.6	1.9		+ 5.6

*Heart volume and stroke volumes were calculated from slit kymograms. The I-J waves were directly recorded displacements of the body.

TABLE II

CONTROL VALUES AND PERCENTAGE CHANGES AFTER NITROCLYCERINE IN SUBJECTS REMAINING ON THEIR FEET DURING THE EXPERIMENT*

Subject	Diastolic Volume Control (ml.)	Change in 6 min. (%)	Stroke Volume Control (ml.)	Change in 6 min. (%)	Heart Rate Control (Beats/min.)	Change in 6 min. (%)	Minute Volume Control (ml.)	Change (%)
Normals								
N	905	-22	56	- 5	92	0	5120	- 5
D	715	-11	52	-19	100	- 8	5200	-25
B	782	- 6	48	-18	84	+55	4050	+25
KS	720	- 4	26	+11	86	+27	2220	+41
AC	734	-15	33	-15	100	+15	3300	- 3
T	828	-22	49	-22	109	+28	6440	0
Mean	781	-13	44	-11	95	+19.5	4720	+ 6
Angina	1,201	- 2	66	-15	60	+38	3960	+17

*Heart volumes and stroke volumes calculated from slit kymograms.

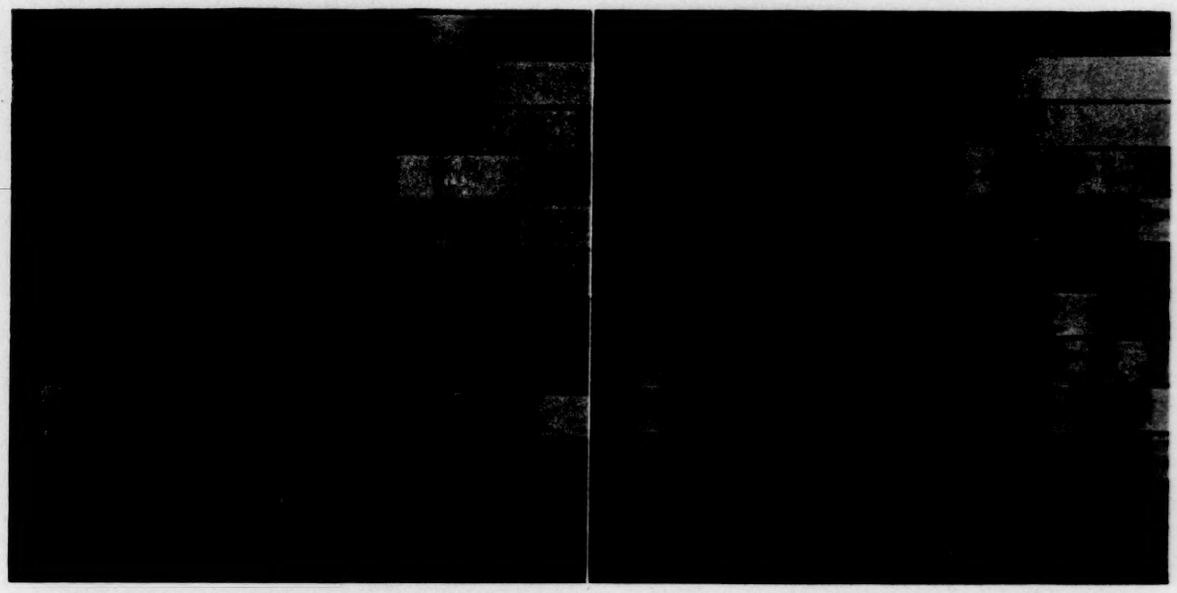

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FIG. 1. The slit kymogram of normal subject N, erect, before nitroglycerine. Estimated volume, 905 cc., stroke 56 cc.

FIG. 2. The slit kymogram of subject N six minutes after 0.6 mg. nitroglycerine. The rate is unchanged, but volume has decreased 22 per cent, stroke by 5 per cent. The white bars are 11 cm. apart in Figures 1 and 2.

of postural effects with sodium nitrite.[4] Minute volume flow rose, with a mean change of +6 per cent in the erect subjects, 13.6 per cent in the recumbent ones. Minute volume fell in two of five recumbent subjects and rose in only two of six erect subjects. On the whole it appears that nitroglycerine increases minute volume flow less than amyl nitrite[1] and, like sodium nitrite,[3] causes variable changes in left ventricular work, with a slight increase in most subjects. Most of the rise is due to acceleration and can be detected in any subject by counting the pulse.

TABLE III

CONTROL VALUES AND PERCENTAGE CHANGES AFTER NITROGLYCERINE IN RECUMBENT SUBJECTS IN WHOM THE DISPLACEMENT AND THE VELOCITY OF BODY MOTION DURING SYSTOLE WERE RECORDED SIMULTANEOUSLY

Subject	Displacement I–J		Velocity I–J			Heart Rate	
	Control (mv.)	Change in 6 min. (%)	Control (mv.)		Change in 6 min. (%)	Control (Beats/min.)	Change (%)
Normals							
T	1.2	+38	8.5		+ 8	88	+11
SN	1.0	+33	4.0	40.5	+38	70	+ 6
D	1.0	+ 6	6.4		-14	61	+22
AC1	1.3	-18	5.1		+12	72	+12
AC2	1.3	-14	6.4	64	+ 4.5	76	+ 7
B	1.4	+10	6.1		+23	70	+10
Mean	1.2	+ 9.0			+11.9	72	+11
Angina	8.6	-16				68	20

The displacement ballistocardiograms taken simultaneously with the kymograms in recumbent subjects (Table 1), with an increase in pulse rate of 22 per cent, showed an increase of

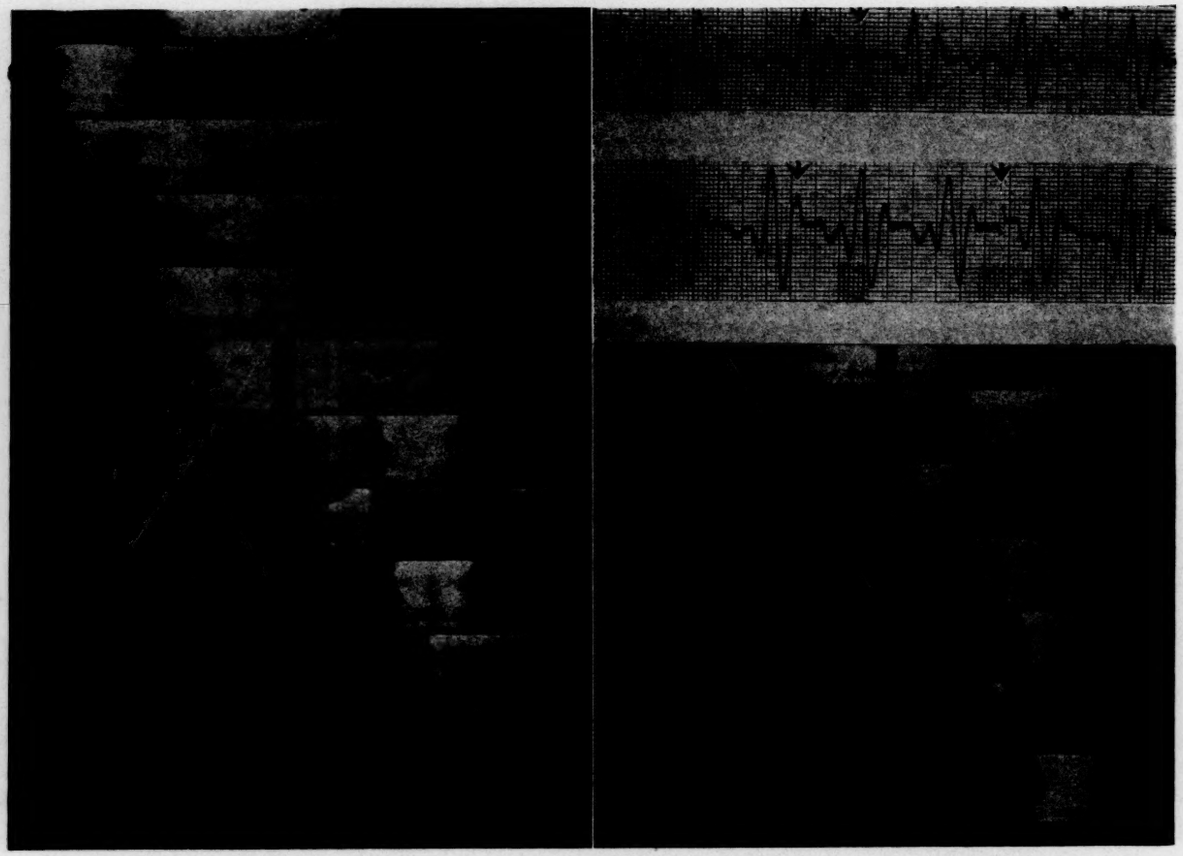

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FIG. 3. The slit kymogram of the left hemithorax of subject Kp, recumbent, before nitroglycerine. White lines are drawn along shadows of the lead cross taped to the chest to center the film. The left border extends 4.9 cm. to the left of this center. The estimated heart volume was 845 cc., stroke 53 cc. The ballistocardiogram is recorded for six seconds, x-ray exposure occurring three to four and a half seconds from the start, as shown by sharp deflection of the base line below the white dots.

FIG. 4. Lower half shows the left hemithorax six minutes after nitroglycerine, the heart border now 4.4 cm. left of the centering cross. Volume decreased only 5 per cent but stroke 10 per cent. Systolic excursion is more abrupt, greater at apex and less in the upper 4.5 cm. than in control film. The upper half shows the control and post-nitroglycerine ballistocardiograms recorded simultaneously with kymograms in Figures 3 and 4. Arrows indicate onset and end of x-ray.

5.6 per cent in the average amplitude of I-J wave which Starr uses as the basis for his calculations of stroke volume.[10] In the tests made later (Table III, Fig. 5), with an average rise in pulse rate of only 11 per cent, the I-J amplitudes of the displacement curves rose 9 per cent; those of the velocity curves rose 11.9 per cent. Only one subject showed a decrease in I-J in the velocity curves, but three of the eleven subjects showed decreases in displacement curves. Two of these were in tests when acceleration was marked; one subject showed this on two tests, several weeks apart, with acceleration of 12 per cent and 7 per cent.

We also studied a case in which the patient had left bundle branch block and angina of effort for three years. Nitroglycerine produced an increase of 20 to 40 per cent in his pulse rate, the higher figure when he was erect. In that position heart volume decreased only 2 per cent and stroke volume 15 per cent. In the recumbent position the amplitude of his displacement I-J waves fell 16 per cent, and his respiratory variation, already large, increased. (Fig. 6.)

COMMENTS

The study of the action of nitroglycerine on the heart using roentgen technics merely confirms the work done by others with the Fick principle and shows that glycerol trinitrate, like amyl and sodium nitrites, accelerates the

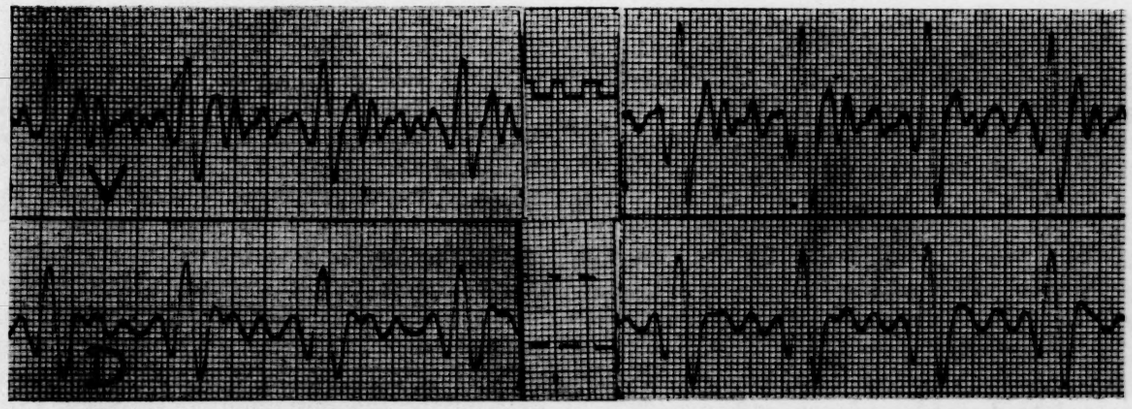

FIG. 5. The velocity (V) and displacement (D) ballistocardiogram of subject B, before (left) and after (right) nitroglycerine; 1 mv. standardization in center. Correcting for relative positions of the standard deflections, J occurs 0.035 seconds earlier in the velocity curve, K occurs 0.045 seconds earlier. Nitroglycerine increases the amplitude of velocity of motion 23 per cent, that of displacement 10 per cent.

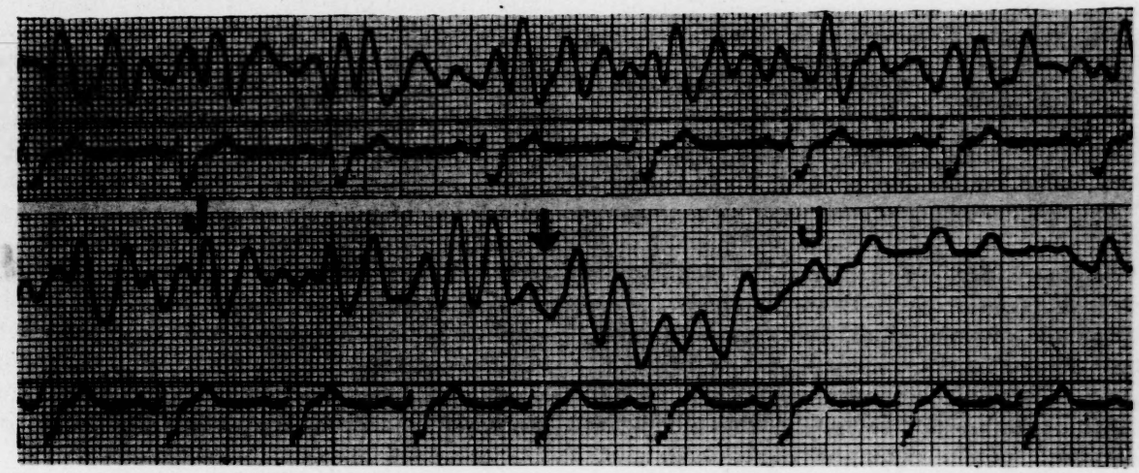

FIG. 6. Above, control ballistocardiogram and electrocardiogram of a man with angina and bundle branch block; below, six minutes after nitroglycerine. The amplitude of I-J varies in control record even though the subject held his breath with the mouth and glottis open. The variation was marked when breathing. At the arrow, patient closed his glottis and involuntarily tightened respiratory muscles without exhaling. Note marked decrease in J wave, disappearance of I. In this subject I-J decreased 16 per cent after nitroglycerine when recumbent; stroke volume, estimated from slit kymograms, fell 15 per cent when patient was on his feet.

heart and decreases heart volume and stroke volume. The net effect on minute volume flow is insignificant in most subjects but may result in a rise of 30 per cent in subjects whose rates are markedly accelerated. The suggestion of Weiss and Wilkins,[4] that the decrease is due primarily to venous pooling and reduced return to the heart is confirmed by the fact that the changes are more marked in erect than recumbent subjects. We made few observations on arterial blood pressure but these confirmed older reports that diastolic pressure is well maintained in spite of a vasodilator action.

If one accepts the evidence of Evans and Matsuoka,[11] Visscher and Starling,[12] and later workers, a decrease in heart volume is associated with a decline in work and oxygen use by the heart at each beat. The decline is proportional to the decrease in volume. Cardiac acceleration raises oxygen use per minute, at constant diastolic volume, about half as much as the percentage rise in rate.[12] A decrease in volume of 10 per cent and rise in rate of 20 per cent might leave oxygen use per minute unchanged.

It is doubtful that these actions of nitroglycerine have any relation to the relief of an anginal attack. Digitalis given to subjects with no heart failure causes a fall in basal heart rate, heart volume and stroke volume but this drug is without value in managing angina pectoris. No

studies have been made on the effect of digitalis on ambulatory subjects but it is probable that during exertion the reduction in venous return is abolished, as is the bradycardia which digitalis produces in recumbent subjects. In that event digitalis would have no effect on angina of effort

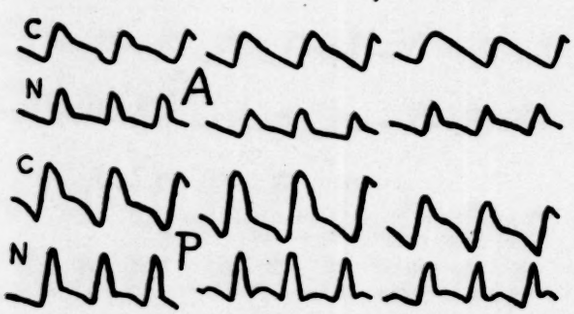

FIG. 7. Tracings of the contours of aortic (A) and pulmonary artery (P) shadows in three corresponding frames of the slit kymograms of subject T, erect, in control (C) and postnitroglycerine (N) films. The sharpness of the systolic wave is increased; the area of the wave section is decreased by nitroglycerine. This subject's blood pressure was not changed by nitroglycerine, but the rate rose from 109 to 140 per minute.

but might reduce the cardiac work of patients with decubital angina. Even in these latter patients, however, digitalis is useless and may even increase the frequency and severity of attacks, although the onset of heart failure with cardiac dilatation and increased work per beat and minute not infrequently relieves angina of both types. It seems reasonable to conclude that angina is not directly related to cardiac work per beat, and that nitroglycerine, which has little effect on work per minute, benefits angina by permitting better flow through the larger coronary collateral arteries. Certainly the drug is not helpful after myocardial infarction since it accelerates the heart and decreases venous return but does not relieve pain.

It is worth noting that nitroglycerine, in normal subjects and in one case of angina, accentuated the respiratory variation in height of the I-J waves of the ballistocardiograph. An increase in this variation is commonly present in anginal patients, as compared with controls of the same age.[13] In those cases of angina in which respiratory variation is decreased by elastic abdominal belts the disorder often is benefited.[14] This suggests that any disturbance in cardiac function due to poor venous return aggravates angina and that nitroglycerine is effective in spite of its action in decreasing cardiac filling.

The action of nitroglycerine on the arterial bed is remarkable and probably explains why the ballistic complexes increase although the stroke volume is diminished. In 1945 Hamilton, Dow and Remington[15] proved conclusively that the amplitude of the systolic waves of the ballistocardiogram was related to the velocity of ejection, rather than the volume ejected. This has been fully confirmed by Starr and his co-workers.[10] The speed with which ejection rises to a peak appears to be all-important in determining the amplitude of I-J. Slight variations in speed of rise may cause a difference of several hundred per cent in I-J amplitude of beats ejecting equal volumes of blood, at constant diastolic pressure.[10] The flush, the throbbing of head and limbs, and the dilated temporal arteries all prove to subjects and observers that nitroglycerine dilates arteries and the venules of the skin. However, blood pressure determined by the auscultatory method shows only minimal and transient change in either systolic or diastolic levels of subjects erect or recumbent, and a fall in systolic levels only in those who are erect. The fact that pulse pressure and diastolic pressure are maintained in spite of a rise in rate would indicate that peripheral resistance might have decreased, since pressure must fall more rapidly in the shortened diastoles in order to keep systolic and diastolic levels the same with shorter cycles.

The curves of aortic and pulmonic arterial pulsation, recorded by slit kymography, change strikingly after nitroglycerine. The systolic spike may be slightly diminished, or it may increase, but its duration is brief. Diastolic fall is completed quickly and the area of the pulse wave is decreased. (Fig. 7.) This fits the evidence recorded by others and the phenomena mentioned previously, indicating that the large vessels are relaxed and the arterial reservoir has increased resiliency. If this is true, resistance to systolic ejection is actually decreased, and speed of initial ejection is high. As a result I-J amplitude rises even when stroke volume is decreased. An increased depth of the K waves was a striking feature in most of our postnitroglycerine curves. (Fig. 4.) This suggests vasodilatation in the splanchnic area or a sharper peak on the wave of flow down the aorta. The increased minute volume flow caused by nitrites is certainly due to a fall in peripheral resistance,

with the arterial pressure maintained in part by the rise in output and in part by cardiac acceleration.

The rise of 27 per cent in mean stroke volume reported by Wegria et al. was based on low frequency table ballistocardiograms and a formula[16] in which stroke varies with I-J amplitude divided by I-J duration. The latter interval is 0.04 to 0.08 seconds, tends to decrease as rate increases with nitroglycerine, and must be measured with a comparator to assure accuracy to ±10 per cent. We attempted no actual calculation of stroke volume but the rise of 12 per cent in amplitude of the velocity I-J wave of our recumbent subjects, and of 100 per cent in an erect subject,[5] may be compared with Wegria's rise of 27 per cent in stroke calculated from mean velocity (I-J displacement divided by I-J interval). In Starr's formula stroke varies with the square root of the displacement I-J amplitude and the fourth root of cycle length. Applied to our data, showing an increase of 9 per cent in displacement I-J, this formula would indicate an increase of less than 3 per cent in mean stroke volume, due to nitroglycerine.

Since calculations based on any type of ballistic study do not correctly indicate the *direction* in which mean stroke volume is changed by nitrites, the most that can be said is that Starr's method seems less fallacious than Nickerson's when applied to this problem. The latter method has been criticized on theoretic grounds by Braunstein et al.[17] It requires accurate measurement of I-J interval and adjustment of spring length to body weight of each subject, so that it is the most bothersome to use.

It may be of interest to compare the effect of maximal exertion with that of nitroglycerine. Subject D had a control stroke volume, by kymography, of 39 cc. When recumbent immediately after running up seven flights of stairs his diastolic heart volume decreased 15 per cent, his heart rate rose 120 per cent, stroke volume 90 per cent, I-J amplitude 460 per cent and I-J/I-J duration 650 per cent. The rise in minute volume indicated by the slit-kymographic method is 320 per cent, about the order of magnitude others have noted using the Fick principle to study the effect of maximal exertion. The rise indicated by I-J height/I-J duration × rate would be 164 per cent, while by I-J height × rate would be 420 per cent. This last formula, which resembles Starr's, does give a reasonable fit.

The Nickerson formula probably would give a reasonable fit if the low frequency, critically damped table were used to study effects of violent exertion. This table was expressly designed to give deflections which vary in amplitude not with the actual motions of the body, nor the force with which the blood acts on the body, but with the volume of blood being ejected. Under normal conditions in normal subjects changes in velocity of ejection closely parallel changes in volume ejected; and since the force varies with the square of the velocity, the low frequency, oil-damped table gives a response roughly proportioned to the square root of velocity of ejection. That is why two very different formulas are used with the two types of recording. Direct recording is similar to high frequency table recording. However, as Hamilton, Dow and Remington clearly proved,[15] no ballistic formula or recording system can be depended upon to yield correct values for cardiac output when it has been altered by drugs, exercise or disease.

In studies of digitalis Starr's method gives the right direction but exaggerates the quantitative effect of digitalis in normal subjects.[18] Thus I-J fell 80 per cent in one of Starr's cases after 1.6 gm. folia digitalis, and stroke volume calculated by the square root formula fell nearly 50 per cent. Stroke volume measured in other human subjects by the Fick principle never has fallen more than 20 per cent under digitalis. Since digitalis raises blood pressure or holds it constant in spite of a decrease in heart rate and stroke volume, it must reduce velocity of outflow from the arterial reservoir and increase resistance to ejection. This results in a ballistic change greater than the change in stroke volume. Nitroglycerine, which reduces volume and increases velocity of ejection, causes ballistic changes opposite to the change in stroke volume in a majority of normal subjects.

CONCLUSIONS

Nitroglycerine, like amyl nitrite and sodium nitrite, given in doses which accelerate the pulse decreases stroke volume and heart volume. The effect on minute volume is variable but the increase is never large with any of these drugs.

The systolic waves of the ballistocardiogram usually increase in amplitude after nitroglycerine. When stroke volume is calculated from mean velocity (I-J amplitude divided by duration), or with the low frequency, critically

damped ballistocardiograph, it seems greatly increased. Maximum velocity during I-J, recorded directly by an electromagnetic pick-up, increases about half as much; the I-J in displacement curves increases even less under nitroglycerine but by all ballistic methods for calculating stroke volume it would appear to be increased even when it actually is diminished by nitrites.

The relation of these facts to the use of nitroglycerine in angina and to the calculation of stroke volume from ballistocardiographic waves is discussed.

It is concluded from this experience that the ballistocardiograph yields misleading data when stroke volume is calculated during action of drugs or diseases which alter duration or force of systole, or the arterial resistance or venous return. This conclusion is in accord with previous observations by others.

The clinical value of the ballistocardiograph lies in its sensitivity to velocity of systolic ejection, which no other method of study duplicates, and not in estimating stroke volume. The slit kymograph may be more useful in estimating the changes in heart volume and in stroke volume occurring under drug action than in absolute measurements of either volume or stroke.

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Renal Function during Emotional Diuresis*

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Emotional diuresis has been observed many times in the past.[1] It has been mentioned, for instance, as being common in anxiety states and vasomotor neuroses and in patients during episodes of tension when undergoing psychoanalysis. Heilig and Hoff,[2] too, in subjects under hypnosis found water, sodium, chloride and phosphate diuresis during suggestions of a disagreeable nature and retention of the same substances when the suggestion was pleasant. This was largely confirmed by Grossman[3] although the reverse response was noted in two subjects. Marx,[4] by suggesting to hypnotised subjects who had been deprived of fluid for twelve hours that they were being given drinks, was able to provoke a diuresis beginning in twenty minutes which caused a fall in urinary specific gravity from 1.025 to 1.002. Stutzin[5] observed diuresis and vigorous ureteric peristalsis during cystoscopy of a nervous and uncooperative patient, with return to the normal state following reassurance. Marx[6] was able to establish by conditioned reflex diuresis in a dog deprived of water for fifteen to eighteen hours; this diuresis was similar in volume to that which followed a fluid feed, and the specific gravity was about 1.007. In general, the existence of emotional diuresis is well established but there are insufficient data for understanding its mechanism.

The patient to be described was admitted for assessment of her hypertension. A conspicuous diuresis was noticed during one of her investigations. Repetition of the procedure, with a similar diuresis, convinced us that it could only have been emotionally induced. Various observations are presented which throw some light on its nature.

HISTORY AND PHYSICAL FINDINGS

W., aged fifty-two, a housewife, was admitted in January, 1951, for investigation of hypertension. She was anxious to undergo surgical treatment despite complete absence of symptoms since placed on a low salt diet nine months previously. A raised blood pressure (240/140 mm. Hg) had first been noted in 1943 when admitted to another hospital, following haemoptysis. No other cause for this bleeding was found. Since then the patient had been symptom-free until 1949 when she began to suffer from headaches and "giddy attacks" which persisted until she started the low salt regimen. This she had adhered to strictly, even baking her own bread for the purpose.

There was no past history of nephritis or toxaemia of pregnancy. Her mother had been hypertensive.

On examination the patient was a cheerful, plumpish person who took an enthusiastic, almost obsessional, interest in her diet and investigations. There was no oedema and the jugular venous pressure was not raised. She was not orthopnoeic. The pulse rate was 70 and the rhythm regular. The apex beat was in the 6th intercostal space in the anterior axillary line. There were no thrills. A loud apical systolic murmur was heard. There was no triple rhythm. The blood pressure varied between 220/110 and 275/160 mm. Hg. No alternation was noticed. In the retinae some arterial narrowing and venous nipping was observed but no exudates, haemorrhages or papilloedema. There was no hirsutes or other suggestion of endocrine imbalance.

Miscellaneous investigations included urine analysis as follows: urine, normal deposit, no sugar and a trace of protein. Blood urea on January 8, 1951, was 31 mg. per 100 ml. and on February 2nd was 34 mg. per 100 ml. Serum sodium on January 10, 1951, was 149 mEq./L.; February 8th, 147 mEq./L.; February 12th, 156 mEq./L. and February 16th, 155 mEq./L. Serum potassium on January 10, 1951, was 2.9 mEq./L.; January 15th, 3.05 mEq./L.; February 2nd, 3.0 mEq./L. and February 16th,

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3.45 mEq./L. Twenty-four-hour urinary sodium excretion on January 10th was 11 mEq. Twenty-four-hour 17-ketosteroid excretion on February 18th was 5.2 mg. Electrocardiogram was within normal limits. X-ray of the heart showed a "finely granular." The heart was grossly enlarged and weighed 595 gm. (normal 250 gm.). No comment was made about the pituitary and adrenals which were probably not specially examined.

TABLE I

DATA OBTAINED BEFORE AND AFTER THREE CYSTOSCOPIES AND THE SECOND WATER LOAD TEST

Date			Jan. 18, 1951		Feb. 1, 1951			Feb. 6-7	7-8	Feb. 8, 1951			Feb. 12, 1951	
Investigation			1st Cystoscopy		2nd Cystoscopy			3rd Cystoscopy					Second Water Load Test	
		Period	Before	After I II	Before	After I	After II	Before Day I	Day II	After I	After II	After III	Before	After
PAH Clearance (ml. per min.)				394 364		425	404							
Renal Blood Flow (ml. per min.)				716 662		774	734							
Inulin Clearance (ml. per min.)				76 81		74	71							
Filtration Fraction				0.19 0.22		0.17	0.18							
Creatinine Clearance (ml. per min.)					30	69	68	40	53	80	92	79	27	70
Urine Flow (ml. per min.)				9.1 8.0	1.9	12.6	12.8	1.2	0.9	5.2	18.2	6.5	0.5	14.9
Water Reabsorbed (ml. per min.)				67 73	28	56	55	39	52	75	74	73	26	55
Inulin U/P Ratio				8 10		6	5.5							
Creatinine U/P Ratio					16	6	5	33	59	15	5	12	54	5
Urinary Concentration	Na (mEq./L.)				82	114	114	21	21	69	81	102	7	30
	Cl (mEq./L.)				57	69	74	22	24	60	79	96	12	28
	K (mEq./L.)				3.2	1.6	1.5	3.0	4.7	4.9	1.4	2.5		
	PO_4 (mg./%)							119	158	34	20	23	84	15
	Urea (mg./%)							925	1530	455	188	347	965	158
	Total Solids (mg./%)							1714	2800	1216	852	1260	1872	414
Excretion Rate	Na (μEq./min.)				156	1430	1460	25	19	358	1470	664	4	447
	Cl (μEq./min.)				106	870	947	26	22	312	1440	623	6	418
	K (μEq./min.)				6.1	20	19	3.6	4.2	25	25	16		
	PO_4 (mg./min.)							1.4	1.4	1.8	3.6	1.5	0.4	2.2
	Urea (mg./min.)							11	14	24	34	23	5	24

moderate left ventricular enlargement. Intravenous pyelogram revealed good excretion of both kidneys. The right pelvis and calyces were duplicated; the left side was normal.

Everything pointed to a diagnosis of essential hypertension except for the anomalous but consistently high serum sodium and low serum potassium. This finding was all the more unexpected because of the low salt diet which the patient had been on for some months and which she continued to take during her hospital stay. This hospital diet contained about 25 mEq. of sodium per day.

Investigations were made over a period of six weeks; no surgical treatment was performed and the patient was then discharged. A few days later she died suddenly; and at a postmortem, arranged elsewhere to establish the cause of death, a subarachnoid haemorrhage was found arising from an atheromatous anterior communicating artery. There was no intracranial aneurysm. The kidneys were described as

EMOTIONAL DIURESIS

The particular interest in this patient lay in the occurrence of a brisk diuresis on three occasions following cystoscopy when she was in a dehydrated state, and on another occasion during a water elimination test although she had previously shown a poor response to a similar water load. These unexpected diureses, we believe, by exclusion, were emotionally conditioned. The three cystoscopy investigations and two water diuresis tests are reported in detail.

Procedure. The procedure in the three cystoscopies differed in the way described as follows: First cystoscopy: The patient had been without fluids for twenty hours. Inulin and PAH clearances were estimated during the subsequent diuresis. Second cystoscopy: The patient had been without fluids for twenty-one hours. Urine was collected for the two hours preceding the cystoscopy. Creatinine clearances and sodium, chloride and potassium concentrations in the

urine were estimated before and after the cystoscopy. Inulin and PAH clearances were also estimated but only after the cystoscopy. Third cystoscopy: The patient on this occasion was deprived of fluids for twenty-seven hours. Urine was collected during this period and and Taussky's[10] modification of Folin's method; blood urea by the method of van Slyke and Cullen as quoted by Peters and van Slyke;[11] urine urea by the hypobromite method; urine total solids by evaporating and desiccating known volumes of urine to constant weight.

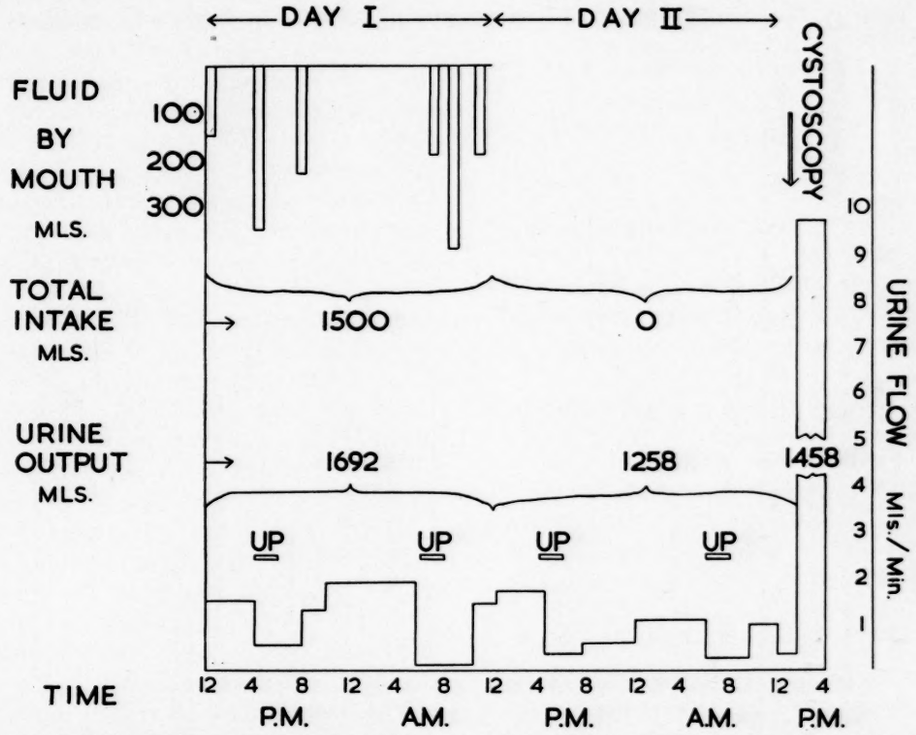

FIG. 1. Urine flow and total fluid intake and output for two days before and two and a half hours after the third cystoscopy.

during the preceding twenty-four hours in which the fluid intake was 1,500 ml. Creatinine clearances and urinary concentrations of Na, Cl, K, PO_4, urea and total solids were estimated for the two days preceding the cystoscopy and also during the subsequent diuresis. Plasma sodium and chloride were estimated before and after the cystoscopy.

Methods. Inulin and creatinine clearances were taken to equal the glomerular filtration rate, and the PAH clearance the effective renal plasma flow. Administration and chemical estimation of inulin and PAH have been described elsewhere.[7] The priming infusion was given after the onset of the diureses. Sodium and potassium were determined by flame photometry with lithium as an internal standard; chloride by the iodometric method of van Slyke and Hiller;[8] inorganic phosphorus by the method of Briggs[9] and then expressed as PO_4; creatinine by Bonsnes

Heparinized venous samples were taken at the mid-point of each clearance period. In the diureses following the cystoscopies the urine was collected through a multiholed urethral catheter. In the water elimination tests the urine was passed naturally.

Results. Tabulated results are shown in Table 1.

Rate of urine flow: All three cystoscopies were followed with a pronounced increase in urine flow, the highest rates recorded for each being 14, 18 and 18.2 ml. per minute. (These peak flows after the first and second cystoscopies are higher than the flows shown in Table 1 since the clearances and observations on urinary constituents were made when the diuresis was subsiding.)

Most data were recorded before and after the third cystoscopy, as is shown in detail in Figures 1 and 2. Figure 1 shows the rate of urine flow

for the two days before the third cystoscopy contrasted with the rate of urine flow throughout the subsequent diuresis. During the first of these days 1,500 ml. of fluid was taken and during the second, none. Figure 2 shows in detail the fluctuations in the rate of urine flow in urine collection. We tried to correlate them with changes in the patient's mood but were unable to do so. During the first twenty minutes she was rather sullen, apparently resenting the presence of a student. For the next eighty minutes she was cheerful, laughing and chatting

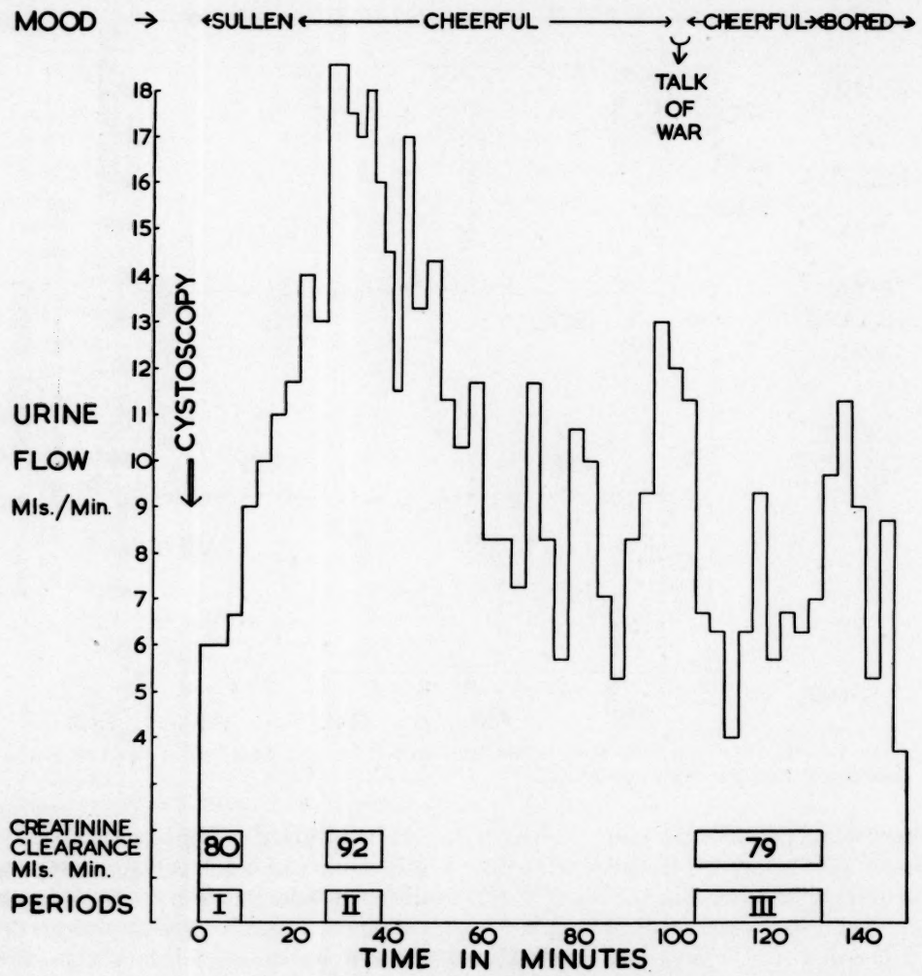

Fig. 2. Urine flow following third cystoscopy.

during the diuresis, the urine being collected at two or three minute intervals. It will be noticed that during the twenty-seven hours preceding the cystoscopy the urine flow did not exceed 2 ml. per minute. Only 1,258 ml. of urine were passed in this time whereas after the cystoscopy as many as 1,458 ml. of urine were passed in two and a half hours with an average flow of 9.7 ml. per minute. Although the urine flow was falling off, the diuresis was still in progress when the investigation was terminated two and a half hours after the cystoscopy. The fluctuations in urine flow we believe were not due to difficulties incessantly with the nurse. A deliberate discussion about her frightening war experiences of bombs and "doodlebugs" was followed by a drop in urine flow, but this was hardly more impressive than previous unexplained falls.

Endogenous creatinine, inulin and PAH clearances: During the diureses there was a pronounced rise in creatinine clearance, from 30 to 69 ml. per minute in the second cystoscopy and from 53 to 92 ml. per minute in the third. The initial levels were well below normal. The inulin clearances were performed only during diuresis and agree substantially with the creatinine clearance:

$$\frac{C_{CR}}{C_{IN}} = 0.94$$

PAH clearances again were performed only during the diuretic periods and show values slightly below normal. During the diureses the filtration fraction was 0.17 and 0.18. As this is a low figure for a patient with gross hypertension, it is unlikely to have been lower in the period before the diuresis (i.e., if the plasma flow was the same before and during the diuresis, the filtration fraction before would have to have been about 0.07, an unlikely figure in the circumstances.) With this assumption it therefore follows that at least a commensurate rise in renal plasma flow accompanied the rise in glomerular filtration.

Inulin and creatinine U/P ratio: During diuresis there was a fall in the inulin and creatinine U/P ratio, from 16 to 5 in the second cystoscopy and from 59 to 5 in the third. This indicates that a decreased proportion of the glomerular filtrate was reabsorbed during the diuresis. Nevertheless, during the same period the absolute amount of water reabsorbed per minute increased from 28 to 56 ml. per minute after the second cystoscopy and from 52 to 75 ml. per minute after the third.

Specific gravity: Two days before the third cystoscopy, when the fluid intake was 1,500 ml., the mean specific gravity of the urine was 1.006. The day before when there was complete fluid deprivation the specific gravity rose to 1.013. At the peak of the subsequent diuresis the specific gravity fell to 1.003.

Urinary concentration and excretion rate of sodium, chloride, potassium, phosphate and urea: The changes which occurred during the diureses were as follows: (1) A great increase in sodium and chloride excretion with *increased* urinary concentration, e.g., after the third cystoscopy the concentration of sodium rose from 21 mEq./L. to 102 mEq./L. and the excretion rate from 19 μEq./minute to 1,470 μEq./minute; (2) a definite but smaller increase in potassium, phosphate and urea excretion with *decreased* urinary concentration.

Plasma levels and tubular reabsorption of sodium and chloride: The plasma sodium level was 147 mEq./L. on the morning preceding the third cystoscopy, and 156 and 155 mEq./L. during the subsequent diuresis. The corresponding plasma chloride levels rose from 101 mEq./L. to 108 and 110 mEq./L.

Assuming that the creatinine clearance equals glomerular filtration and ignoring the Donnan equilibrium effect, the total quantity of sodium reabsorbed by the tubules and the percentage reabsorption rate can be calculated from the following formulae:

(I) Sodium reabsorbed = sodium load (i.e., $C_{CR} \times$ plasma Na) − sodium excreted

(II) Per cent sodium reabsorbed

$$= \frac{\text{sodium load} - \text{sodium excreted}}{\text{sodium load}} \times 100$$

It follows that:

Sodium reabsorbed before third cystoscopy = 7,772 μEq./minute

Sodium reabsorbed at height of third cystoscopy diuresis = 12,760 μEq./minute

Per cent sodium reabsorbed before third cystoscopy = 99.8%

Per cent sodium reabsorbed at height of third cystoscopy diuresis = 89.6%

Parallel changes can be shown for total and percentage chloride reabsorption. In both, during diuresis, there was a substantial increase in *total* and a decrease in *percentage* reabsorption.

EMOTIONAL DIURESIS DURING WATER LOADING

Soon after admission a routine investigation was performed to test the response to water load following twelve hours fluid deprivation. The bladder was emptied; 1,420 ml. of water were given by mouth and hourly samples of urine collected for the subsequent four hours. A month later, following the three cystoscopies, a second water load test was performed. On this occasion no fluid had been taken for sixteen hours. The urine formed during the four hours before the test was first collected, then 1,000 ml. of water were given and followed by 300 ml. at thirty minute intervals throughout the test. The urine was collected in half-hour periods for two and a half hours. Creatinine clearances and the urinary concentrations of sodium, chloride, phosphate, urea and total solids were estimated before and during the test.

Result. The results of the first test are shown in Figure 3A; those of the second, in Figure 3B and Table I.

Unfortunately, as the methods of water loading in the two tests were different, only the first hour of each test is comparable. For that hour the water loads were 1,420 and 1,300 ml.

and the amounts passed 114 ml. (urine flow 1.9 ml. per minute) and 624 ml. (urine flow 10.4 ml. per minute), respectively.

In the second test the increase in the creatinine clearance and sodium and chloride excretion was similar to that following the cystoscopies.

emotion is less clear, although anxiety seems the most likely. If this were so, it was scarcely on a conscious level and was not attached to the investigations, which indeed she seemed to enjoy for the kudos involved, but more plausibly was connected to her mental associations of "high

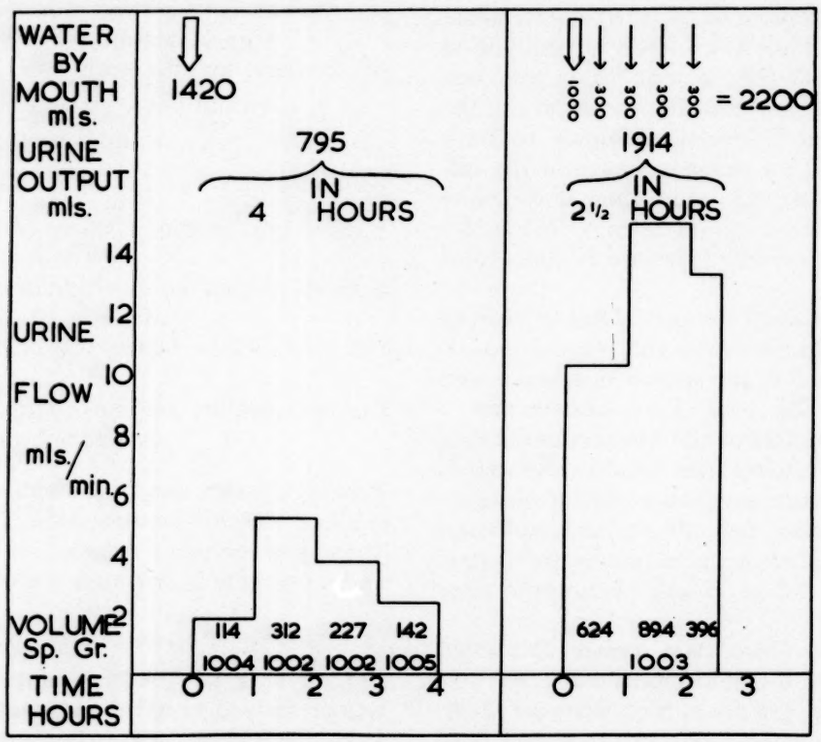

FIG. 3. Urine flow and fluid intake in two water load tests. A, first test performed soon after admission; B, second test a month later.

Observations. In the first test there was a considerable limitation of water excretion. In the second there was, on the contrary, an abnormally early and profuse diuresis. It is considered that the most likely explanation for this anomaly is that the second water diuresis was partially emotional in type. The creatinine clearance and sodium and chloride excretory changes in the second test are consistent with this suggestion.

COMMENTS

Following periods of twelve to twenty-seven hours fluid deprivation this patient passed large quantities of water and salt in her urine. We consider that this phenomenon was emotionally induced. It seemed to us that during her stay in the hospital she became so "sensitized" that any investigation produced a diuresis of this type (e.g., second water diuresis). The nature of the blood pressure" and the premonition of surgery which these investigations evoked. During the diureses the patient's outward behaviour was unruffled and her pulse unchanged, although her blood pressure was perhaps a little higher than usual.

Before discussing the mechanisms of these diureses it must be emphasized that this patient's basic renal function was not normal. The paradoxic way, however, in which her renal functional efficiency, as judged by clearance studies and water elimination, improved under emotional strain made these usual criteria for assessing the extent of functional capacity valueless. She had severe hypertension, and it has been shown[12,13] that with increased rates of urine flow subjects with hypertension have a special propensity for excreting greater than normal amounts of sodium chloride; although in the

cases described, the urinary concentration fell. Further, a diminished glomerular filtration is known to be associated with a low salt intake.[13,14]

The outstanding features of all the diureses were the high urine flow, the increased output of sodium and chloride, and the increase in glomerular filtration rate. A decrease in the proportion of tubular water reabsorbed accompanied the rise in urine flow, as evidenced by the fall in specific gravity below 1.010 and the fall in creatinine U/P ratio. At the same time, however, there was a rise in the total water reabsorbed. Tubular function as regards sodium and chloride followed a similar pattern, the percentage tubular reabsorption falling by 10 per cent although the total reabsorption was doubled.

The results of the PAH and inulin clearances suggest that the increase in glomerular filtration rate was probably associated with renal vasodilation. The fall in percentage water reabsorption can be explained by either (1) the capacity of the tubules to reabsorb water being exceeded by the rise in glomerular filtration, (2) posterior pituitary inhibition or (3) a combination of these two. A combination seems the most probable. We do not believe that the first can have been the whole explanation as the specific gravity of the urine fell below 1.010. Although posterior pituitary inhibition probably occurred, we do not consider that it was responsible for the rise in glomerular filtration and presumed vasodilation. There may sometimes be a raised glomerular filtration rate when posterior pituitary inhibition is associated with overhydration and increase of blood volume, but in this case there was *dehydration* and probably a diminished blood volume. Strauss et al.[15] found no increase of glomerular filtration in man during inhibition of the posterior pituitary with alcohol, nor did Verney,[16] in dogs, find water diuresis to be associated with an increase in renal blood flow.

The decrease in percentage reabsorption of sodium chloride may also have been due to (1) the rise in glomerular filtration rate overloading the tubular capacity to reabsorb sodium chloride, (2) an inhibition of some salt retaining hormone or (3) a combination of the first and second. The rate at which the salt excretion increased makes it unlikely that hormonal inhibition was the main factor concerned. Tubular overloading seems the probable explanation especially as it is established that in hypertensives an increase in urine flow is associated with excess salt excretion.[12,13]

We would suggest that as a result of emotion a simultaneous nervous renal vasodilation and posterior pituitary inhibition occurred. This caused an increased glomerular filtration rate and water excretion which in the presence of abnormal tubules caused a pronounced increase in salt excretion. Borst[17,18] has described in normotensives and under varied circumstances a water and salt diuresis occurring with or without a simultaneous increase in glomerular filtration; he suggests that this diuresis is brought about by certain circulatory changes stimulating some central effector mechanism. An emotional stimulation of this hypothetic effector may have occurred in our case.

SUMMARY

An impressive water, sodium and chloride diuresis is described occurring in a hypertensive subject in response to emotion. Observations were made upon the creatinine, inulin and para-aminohippurate clearances and upon various urinary constituents.

An increase in glomerular filtration and a diminished percentage reabsorption of water and salt occurred.

It is suggested that the increase in water excretion was due to simultaneous nervous renal vasodilation (with raised glomerular filtration rate) and posterior pituitary inhibition. The increase in salt excretion probably also resulted from the raised glomerular filtration rate, and was accentuated by hypertensive tubular inadequacy.

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Forced High Caloric, Low Protein Diet and the Treatment of Uremia*

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UREMIA, a common medical problem, remains a therapeutic stumbling block. Its treatment is often neglected for the reason that the underlying disease is considered hopeless. Inasmuch as dietary management of nauseated uremic patients is difficult it is often not considered worth while. However, in Amsterdam in 1946 Borst[2,3] proved that a diet containing practically no protein but providing enough carbohydrates and fats to cover caloric requirements could reduce endogenous protein catabolism to a degree not realized previously (except by Kempner[14]).

This opened new possibilities for the treatment of uremia. A patient with chronic impaired kidney function now may be in urea equilibrium as long as he is able to excrete 2 to 5 gm. of urea per day. It was calculated by Borst that an anuric patient on his diet who accumulated all the urea that he produces might live for twenty-three days before his blood urea would rise to 350 mg. per 100 ml., a figure compatible with life.

This report is intended to describe the effects of the forced high caloric, low protein diet in the treatment of uremia, to illustrate this with abstracts of selected cases and to provide the physician with an outline of dietary suggestions which make such treatment less tedious and impractical.

The treatment of uremia depends in part on the natural history of the underlying renal disease which will not be discussed. Although certain principles of treatment apply both to acute anuric uremia and to uremia of chronic renal impairment, it is easier for practical reasons to consider them separately. The acute exacerbation of chronic uremia should be treated as acute uremia with anticipation that a condition of relative urea equilibrium may result. As any benefit from dietary measures may be nullified by mismanagement with water and electrolytes, an outline of presently accepted concepts is presented.

ACUTE ANURIC UREMIA

The general principles underlying treatment of acute anuric uremia are as follows: (1) *Regulation of fluid and electrolyte balance, the most important features of which are* avoidance of excessive amounts of water and salt during the anuric phase, supply of both in the diuretic phase; prevention or correction of severe acidosis and prevention of hyperpotassemia. (2) *Suppression of protein catabolism which in turn suppresses the formation of retention products:* omission or a sharp reduction of protein intake; suppression of endogenous protein catabolism with forced high caloric non-protein diet; prevention or treatment of present infection with antibiotics; avoidance of operations (decapsulation) which promote protein breakdown. (3) *Avoidance of excessive amounts of water and salt:* pulmonary edema is still the most common cause of death in acute uremia and is frequently contributed to by the physician. "The body is not analogous to a tank into which water can be forced until it finally bursts out through the kidneys."[22]

The importance of rigid fluid and salt restriction in the treatment of acute anuric uremia has been recognized only in the last few years (Lattimer,[22] Bull and Joekes,[4] Burnett,[5] Thorn,[32] Strauss,[31] Muirhead,[25,26] Stock,[30] Snapper,[29] Kolff,[18,19] Leiter et al.[23] and Friedberg[9]). The water intake should not exceed the insensible water loss while water lost with diarrhea, vomiting and the small amount of urine that may be formed can be allowed for. It is my impression that insensible water loss in patients with edema is not as high as in normal people. Water intake should, therefore, be restricted to 750 ml. per day and salt given only in the amounts which

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are demonstrably lost. In these patients excess of water and salt will not only cause generalized edema but also pulmonary edema, hypertension, cardiac failure and convulsions. These results were apparent in a patient deliberately treated with water and salt by Hoffman and Marshall.[12]

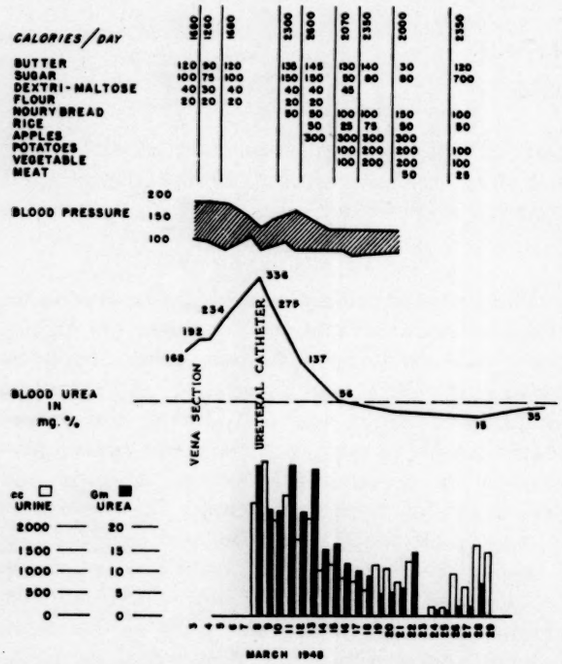

FIG. 1. A woman aged forty-eight experienced anuria following operation for renal calculus. Symptoms of so-called acute uremia disappeared under fluid restriction and forced high caloric diet notwithstanding rising blood urea. Diuresis set in on the tenth day.

They reported that in spite of satisfactory urinary excretion and well established edema, the serum non-protein nitrogen concentration rose from 176 mg. per 100 ml. on the fifth day to 243 mg. on the ninth day. The blood pressure on the ninth day was 180/118 and uremic symptoms were evident, as were those of heart failure. The patient died on the tenth day.

In treatment of a patient with anuric uremia who has been subjected to an excess of intravenous infusions or transfusions, venesection should be performed and 500 to 750 ml. of blood removed before pulmonary edema becomes evident.

Blood transfusions have been employed too frequently in anuric uremia, as they are rarely indicated. When given only to improve the anemia they frequently overload the circulation and bring the recipient to the borderline of or into pulmonary edema. Replacement transfusion[1] in which blood or concentrated red cells are administered while a similar volume of the patient's own blood is removed can restore the hemoglobin without overloading the circulation.[18]

The following case report illustrates some of these points: An obese woman of forty-eight had experienced a left nephrectomy fifteen years previous to observation. On February 27, 1948, an infected stone was removed from the right pelvis. After the operation anuria set in and the patient was encouraged to drink water. In addition, 8 L. of 0.9 per cent NaCl was infused in seventy-two hours. She was admitted to my service on the fourth day of the anuria. She was drowsy, confused and edematous; pulse was rapid and irregular, blood pressure was 190/100, nose and hands were cold and cyanotic. The veins in the neck were distended. Rales were heard at the bases of the lungs. Undoubtedly, heart failure had been provoked by overloading of the circulation. Five hundred cubic centimeters of blood were removed. Fluid was restricted to 750 cc. per day. Low serum bicarbonate content was treated with 10 gm. of sodium bicarbonate. As the blood urea was only 168 mg. per cent, there was no reason for dialysis. As indicated in Figure 1, approximately 1,600 calories were given daily, primarily in the form of butter and sugar. Although the blood urea rose from day to day, the manifestations formerly considered to be part of the clinical picture of acute uremia disappeared. On the tenth day the patient was mentally alert, had no cardiac failure and the blood pressure had dropped to normal; the acidotic breathing had disappeared. The same day ureteral catheterization proved successful and diuresis set in.

Prevention and Correction of Acidosis. Insofar as starvation contributes to uremic acidosis, the fundamental studies on the life raft ration by Gamble[10] and his group should be remembered. One hundred grams of glucose per day will probably prevent starvation ketosis and 50 gm. are almost as effective. This substantiates Strauss'[31] recommendation of a daily intravenous injection of 750 cc. of a 15 per cent glucose solution. The diet discussed in this article also prevents starvation ketosis.

Although it is generally assumed that alkali should be given, Bull, Joekes and Lowe[4] "are uncertain of the importance of deficiency of chloride and bicarbonate but find it impossible to correct anion deficiency without at the same

time introducing excessive quantities of cation." All their cases of protracted anuria showed disturbances of chloride and bicarbonate balance which, however, did not prevent the onset of diuresis. Sodium bicarbonate should be reserved for severe acidosis (serum bicarbonate content lower than 25 volumes per cent) and an attempt should be made to maintain the alkali reserve rather than to correct it. Six to 12 gm. of sodium bicarbonate per day may be necessary in some cases.

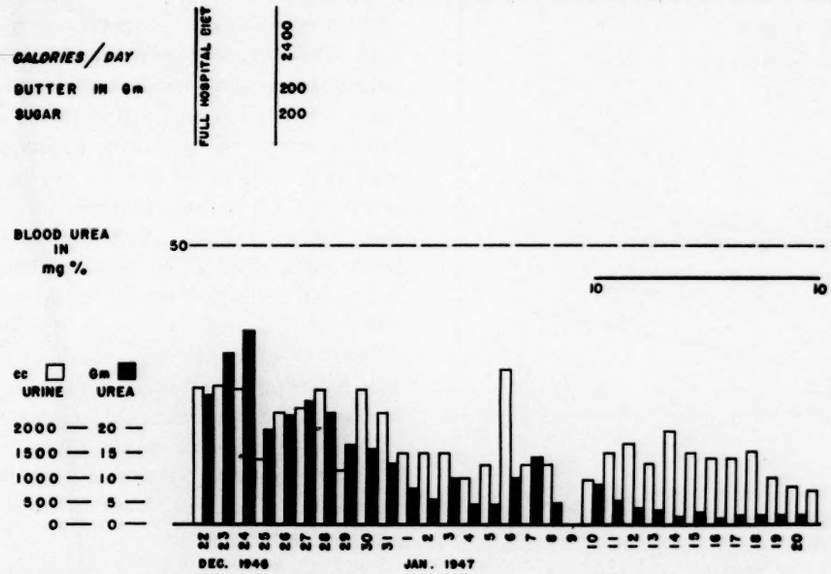

FIG. 2. A man with normal kidneys lived exclusively on 200 gm. of butter and 200 gm. of sugar, 2,400 calories per day for twenty-seven days. Not until the tenth day was the urea excretion reduced to 5 gm.; after twenty days, however, it was less than 2½ gm. per twenty-four hours.

Prevention of Hyperpotassemia. The Borst regimen[3] in its most rigid form is practically free from potassium. When protein catabolism is slowed by a forced high caloric intake, the transfer of cell potassium into serum is prevented. Moreover, a high carbohydrate uptake actually reduces the serum potassium and promotes potassium uptake by the cells.[17]

Suppression of Endogenous Protein Catabolism with a Forced High Caloric Non-protein Diet. The essential difference between Borst's technic[3] and that of all other regimens advocated for the treatment of uremia is the prevention of starvation. The patient is forced to consume the calories prescribed from day to day, hence the term *forced* high caloric low protein diet.

Two students who subsisted on a diet consisting principally of 200 gm. of butter and 200 gm. of sugar per day reduced their daily urea excretion from 22 to 5 gm. On such a diet another man, and many of our patients with chronic nephritis, reduced their daily urea excretion to 2.5 gm. or even less. It requires an interval of time for equilibrium to be established. (Fig. 2.) The minimum levels are reached earlier and are lower in patients whose protein supply is already depleted. Bull, Joekes and Lowe[4] have constructed a graph (Fig. 3) which demonstrates the slow rise in blood urea in a hypothetical patient who retained all his urea (anuria) in comparison with patients not on regimen.

From clinical experience it appears that creatine and uric acid production are also reduced by the high caloric, low protein diet, although perhaps to a lesser degree than urea production. The xanthoprotein reaction continues to rise and does not seem to be influenced. Evidence that this kind of diet will prolong the life of experimental animals is meager, but Masson, Corcoran and Page[24] showed that rats on a high carbohydrate and high fat diet lived longer after nephrectomy than rats on a meat diet or starved.

Practical Application of Diet. In patients who are nauseated and in severe uremia, we usually start the forced high caloric diet with butter and sugar. This can be administered in the form of frozen butter pills eventually filled with sugar or as butter soup. This butter soup is a creamy

emulsion of butter, sugar and a little flour flavored with a strong coffee extract and may be taken hot or cold. More extensive instructions are given concerning variations of this diet on the following pages.

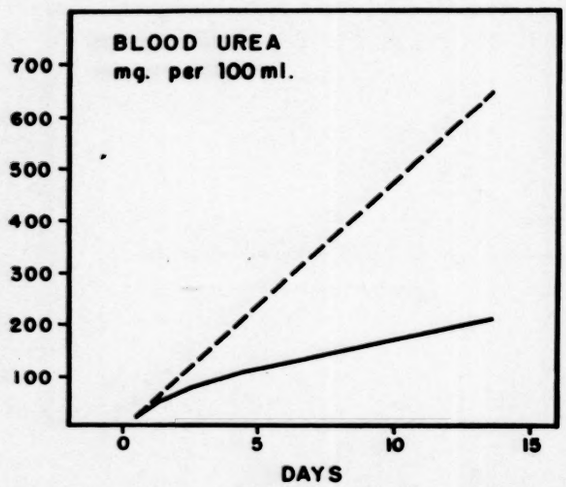

FIG. 3. Mean data on nitrogen metabolism in five controls. Dotted line represents usual rate of rise of blood urea level in anuric patients on regimen. Continuous line represents rate at which blood urea level would rise in anuric patients on regimen. Calculated by assuming retention of daily urinary nitrogen output. (From BULL, JOEKES and LOWE, *Lancet*, 2: 229, 1949.)

It is essential that the importance of the caloric intake should be explained to the patient, the nurse and the family. The patient must be warned that he may vomit from time to time, but with continuance of the diet the vomiting usually decreases. He should be urged to take the butter soup at regular intervals, but more than one cup should not be left on the bedside table. A report of the following four cases may show the practicability of the diet in acute glomerular nephritis:

Figure 4A shows the course of a man thirty-four years old with acute glomerular nephritis who was admitted in the oliguric phase of the disease and produced only 500 ml. of urine per day during the first ten days of hospitalization. After a few days he excreted only 6 gm. of urea per day. His urea production was so small that the blood urea never became elevated. After ten days diuresis improved to almost 2 L. His blood pressure fell from 180/80 to 140/80.

Figure 4B also represents a case of acute glomerular nephritis in a man aged thirty-four who had a blood pressure of 220/120, pulmonary edema and elevated blood urea of 72 mg. per cent on admission. A venesection was done. Two hundred grams of sugar and 200 gm. of butter were given daily and fluids were restricted to 700 cc. The blood urea became normal after eight days; the blood pressure gradually fell.

Figure 4C shows the course of a six year old girl with acute glomerular nephritis. She was admitted to the hospital after at least six days of anuria with a blood urea of 365 mg. per 100 ml. and a serum bicarbonate content of 20 volumes per cent. She was placed on a diet of butter, sugar, salt-free low protein bread and fruit. It was estimated that she consumed between 300 and 900 calories per day. Although the anuria persisted for another three days, the blood urea rose to 414 mg.; with an excretion of 1½ to 3 gm. of urea per day it began to fall and declined rapidly when 5 gm. per day were excreted. Note the increase of urea excretion when a full hospital diet was allowed.

The patient in Figure 4D presented an obscure history of what may have been acute glomerular nephritis with anuria. She was admitted to the hospital with severe congestive heart failure accompanied with pulmonary edema which had been aggravated by excessive saline therapy. Her condition seemed so unfavorable that she was treated immediately with the artificial kidney.[15,16] After this therapy her condition improved so much that she was able to take the high caloric diet in increasing amounts, first 300 and later 1,200 calories per day. With an average excretion of 7 gm. of urea per day, the blood urea was reduced to normal and she had an uneventful recovery.

PRACTICAL SUGGESTIONS FOR PREPARING A HIGH CALORIC LOW PROTEIN DIET*

Emulsion for Intragastric Drip (According to Bull, Joekes and Lowe)[4]

Glucose	400	Give as continuous drip through nasal catheter; use plastic tube; 1 L contains 2,500 calories; 25 cc. of Tween 80 may be added according to Grollman; LipoMul-Oral as used by Stare's group is available from the Upjohn Co.
Peanut oil	100	
Acacia	q.s. to emulsify, usually 25 gm.	
Water	to 1 L.	
Vitamins		

Butter Soup (According to Borst)[28]

Sugar	150 gm.	1,775 calories, 2 gm. protein; when divided over 6 portions of 100 ml. each, each portion will contain approximately 300 calories
Salt-free butter	150 gm.	
Flour	q.s. to make emulsion, usually 20 gm.	
Water	approximately 300 gm.	Vitamins must not be forgotten; should preferably be given parenterally.
Coffee extract		

* With the collaboration of Marjorie Curry, B.S. and June E. Thompson, B.S., dietitians.

Method of Preparation of Borst Butter Soup. Mix sugar and flour together. Add enough water to make a paste; add butter; cook in double boiler, stirring constantly. When flour is well cooked and starch taste disappears, drink easily from a cup. It should be served divided over the day; for example 7 A.M., 9 A.M., 11 A.M., 3 P.M., 6 P.M., 9 P.M., each serving 100 ml. If the patient vomits, continue it. If the patient prefers the drink hot, heat only one

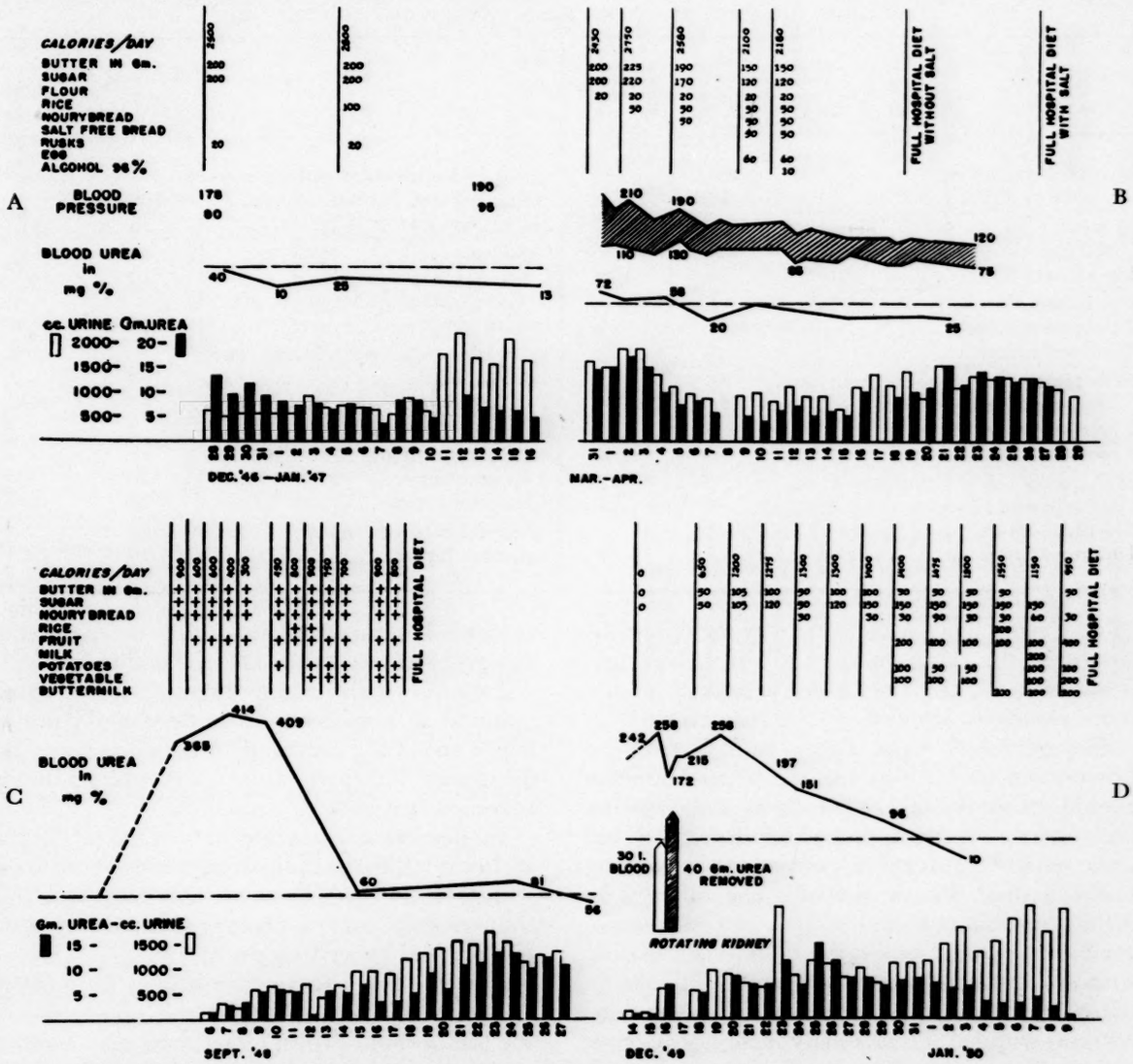

FIG. 4. Patients with acute glomerulonephritis all taking the forced high caloric low protein diet. A, a man aged thirty-four did not develop an elevated blood urea despite oliguria; B, a man of thirty-six whose slightly elevated blood urea rapidly decreased; C, a girl six years old whose high blood urea rapidly declined in spite of oliguria; D, this woman, aged forty-nine, remained well after preliminary treatment with artificial kidney utilized to reduce immediate danger due to overhydration.

gradually add water until total volume is 600 ml. Cook thoroughly, stirring constantly. Remove from heat and cool. Stir until cool; add flavoring. Strong coffee extract is appreciated most, although lemon and vanilla may be tried. If properly made, the Borst butter soup should stay in emulsion, thin enough to portion at a time, otherwise the emulsion may be destroyed.

Chilled Butter Pills. Butter may be made into pills (5 gm. per pill) and frozen. Thirty pills per day would provide 150 gm. of butter or 1,200 calories. One or more of the following suggestions may be used to supplement the butter soup

at the time of the usual meals or given to replace a portion of the butter soup.

Even if all ten of the previous suggestions were given in one day, the patient would get only 22 gm. of protein. If the patient seems to be able to take more food, a diet made of the foodstuffs shown in the table on page 673 may be tried; it is easier to raise the caloric intake if a little more protein is allowed.

DIETARY SUGGESTIONS TO BE USED WITH BORST BUTTER SOUP

	Amount (gm.)	Calories		Amount (gm.)	Calories
½ cupful cooked rice	100		½ cupful boiled sweet potato (contains 200 mg. potassium)	100	
1½ squares butter	15	208	3½ squares butter	35	381
½ cupful baked potato (contains 400 mg. potassium)	100		1 pancake	50	
1½ squares butter	15	198	1 square butter	10	
1 zwiebach (low salt)	8		3 tablespoons syrup (maple or white sugar syrup)	40	322
2 teaspoons jelly	10		½ cupful chocolate pudding (4.5 gm. protein)	100	
½ square butter	5	91	1 tablespoon whipped cream	15	282
fresh tomato puree (canned may be used if salt is allowed)	75		cinnamon toast 1½ slices bread (4.5 gm. protein)	45	
1 teaspoon sugar	5		2 squares butter	20	
3 squares butter	30	265	4 teaspoons sugar	20	341
fresh cooked celery (contains 225 mg. potassium)	75		½ cupful cornmeal mush	100	
3 squares butter	30		2 squares butter	20	221
1 tablespoon cream	15	276			

Feeding through Nasal Tube. Bull, Joekes and Lowe have for various reasons been unable to exceed an intake of 1,000 calories a day giving the butter and sugar diet. Therefore, they fed their patients through a permanent indwelling stomach tube. Plastic polyethylene tubes, 2 to 3 mm. in diameter and without a bulbous tip, are easy to pass through the nose, less irritating than rubber and are much more difficult to disgorge. Through this tube the following mixture is dripped at a steady rate throughout twenty-four hours: glucose, 400 gm.; peanut oil, 100 gm.; acacia q.s., to emulsify; vitamins, optional; water to 1 L.* All vomitus is collected, filtered through lint and returned to the stomach in the same way.

We have used the Bull-Joekes method except for the reinfusion of the vomitus in several cases and found it helpful in many instances. It was an added inducement in urging the patient to persevere in the butter and sugar diet.

Patients with acute uremia have rarely vomited so persistently that they could not be fed in one of the previously mentioned ways. We anticipate the time when fat emulsions for intravenous use will be available.

In desperate cases we have used a cardiac catheter (thin polyethylene tubing) through which 40 per cent of glucose was given as a continuous drip over a prolonged time. At times this method proved successful.[7]

Urea Production Is Not Controlled by High Caloric Diet in Some Cases. Despite the application of the diet a rapid rise in blood urea may occur in patients by factors which cause a breakdown of proteins, for example, severe infections, intoxications (bichloride of mercury), large hematomas, crushing injuries, large operations, eclampsia and extensive hemolytic reactions. Unfortunately, this list is almost identical with the list of the most common causes of lower nephron nephrosis.

The forced high caloric low protein diet will, however, prove valuable when the initial protein

* It may be useful to add polyoxyethylene sorbitan mono-oleate (PSM) or Tween 80[13] from Atlas Powder Company, Wilmington, Del., as an emulsifying agent, probably 25 cc. per L. It has no toxic effect in patients with normal kidney function but the polyoxyethylene fraction is excreted quantitatively in the urine. Grollman[11] used it in patients with impaired kidney functions and in nephrectomized animals. The fat emulsion as advocated by Shoshkes et al.[28] which we recently tried in the treatment of uremia proved to be beneficial. It is manufactured under the name LipoMul-Oral by the Upjohn Co., Kalamazoo, Mich.

breakdown stops. The dialyzing methods, the artificial kidney or peritoneal lavage, may be applied to overcome these severe uremias and improve conditions so that the patients are amenable to dietary treatment.

In the following patient peritoneal lavage[16,18,20] was performed when it became impossible to maintain the diet after thirteen days:

	Amount	Gm.	Calories
Lettuce or tomato or vegetables as carrots, green beans, beets, spinach, asparagus, squash, onions, turnips, broccoli, cauliflower	½ cup cooked	100	20
Mayonnaise	1 tablespoon	15	114
Oil dressing (without salt)	1 tablespoon	15	114
Salt pork or fresh belly	1 slice	50	390
French fried potatoes	10 pieces	55	157
Home fried potatoes	1 medium potato	100	
	2 tablespoons fat	30	300
Fried cornmeal mush	½ cupful sliced and fried with	100	
	3 tablespoons fat	45	400
(Any cereal could be served as fried mush and may be taken with an excess of butter and syrup.)			
Maple or light corn syrup	1 tablespoon	20	50
Marshmallows	1 piece	8	26
Dates, figs, dried fruits	4 pieces	30	90
Apple, peach or cherry pie (higher in salt)	⅙ pie	100	300
Frosted cup cake (higher in salt)	1 medium	55	230
One average commercial candy bar (higher in salt)	2 oz.	55	270
Puffed rice or popcorn (served with syrup)	1 cup	15	100
Only for Patients Who Can Be Allowed More Fluid			
50–200 gm. extra sugar providing up to 800 calories may be given in soft drinks but do not overstep fluid allowance. Kool-Aid, fruit juice, lime, lemon, grapefruit		200	800
Gelatin salad with fruit or vegetable	2½ inch square	155	170
Tapioca pudding (made with milk)	½ cup	100–150	130
Cornstarch pudding (made with milk)	½ cup	140	200
Water ices (commercial)	½ cup	130	147
Sherbets	½ cup	130	247
Ice Cream	½ cup	100	206
Cream soups (canned, if sodium is not restricted)	½ cup	75	100
Extra butter may be added here	1 square	10	80
Baked apple	1 large	115	200
Apple brown Betty	½ cup	130	200
Chocolate syrup	1 oz.	30	75
Cocoamalt	1 tablespoon	9	35

A man fifty-five years of age (Fig. 5) was known to have stones in both kidneys, with severe infection. Repeated and unsuccessful attempts had been made to remove the stones surgically elsewhere. In August, 1947, he experienced a severe urinary infection with high temperature and oliguria. The patient took 200 gm. of butter and 200 gm. of sugar all the time; on the thirteenth day he started to vomit severely. Thereafter, his blood urea, which had been elevating slowly, rose rapidly. A single peritoneal dialysis which removed 53 gm. of urea brought the blood urea down, and fortunately the patient's kidneys opened at the same time.

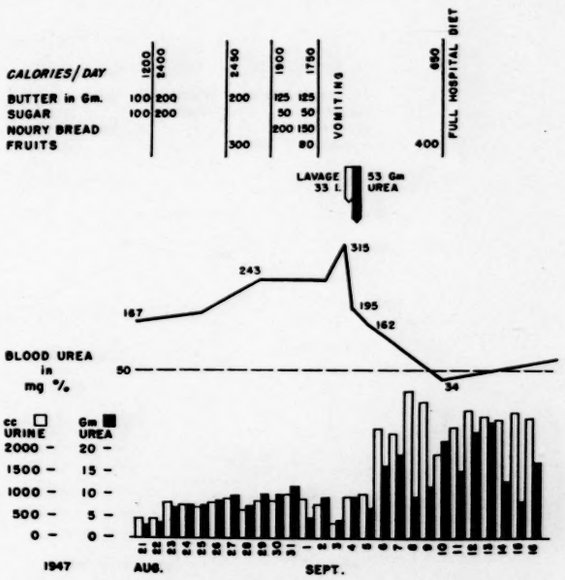

FIG. 5. A fifty-five year old man with nephrolithiasis and recurrent infection was able to take the butter and sugar diet for thirteen days. During that time there was a slow rise of blood urea notwithstanding high fever and an output of less than 10 gm. per day. Diuresis improved suddenly after peritoneal lavage.

CHRONIC UREMIA

The general principles underlying treatment of chronic uremia are as follows:

1. *Regulation of electrolyte and water intake, of which the most important feature is regulation of sodium chloride intake:* salt allowance is determined by the presence of hypertension and edema. Large amounts of salt may be lost. Vomiting may occur if the sodium of the blood plasma is low, and kidney function may be further impaired by lack of sodium. In such cases salt should be given even though the blood pressure is elevated.

2. *Regulation of water intake on a salt-free diet:* not infrequently the patient must be encouraged to drink water but if his contracted kidneys cannot, in the terminal stages, excrete more than 800 to 1,200 cc. of urine per day, it is useless and dangerous to give too much fluid in vain attempt to force the kidneys.

3. *Correction of acidosis:* acidosis may be (partly) prevented by adequate supply of carbohydrates

but sometimes sodium or potassium bicarbonate must be prescribed up to 6 gm. per day.

4. *Homeostasis of potassium:* hyperpotassemia is an infrequent complication when urine output is larger than 1 L. Hypopotassemia is common when chronic uremia is treated with the high caloric low protein diet and may lead to paralysis and cardiac arrest unless corrected with 2 to 6 gm. potassium chloride or bicarbonate per day. Potassium bicarbonate is preferred when the alkali reserve is low.[17]

5. *Control of blood calcium:* low serum calcium may cause or promote nocturnal cramps, tetany or convulsions, especially if acidosis is suddenly corrected. Calcium gluconate 1 or 2 gm. may be given and it may be determined whether removal of phosphates with aluminum hydroxide will improve the condition (basojel® 30 cc. orally four times daily). Magnesium may be too high if laxatives have been used in excess.

6. *Suppression of endogenous and exogenous protein catabolism:* (1) prevention of infection with antibiotics, and (2) suppression of breakdown of body protein by forcing high caloric diet and (3) suppression of exogenous protein catabolism by limiting protein intake to 20 gm. per day while assuring provision of essential amino acids and vitamins.

7. *Occasional transfusion to restore hemoglobin.*

8. *Treatment with artificial kidney or peritoneal lavage* if serious uremia must be overcome.

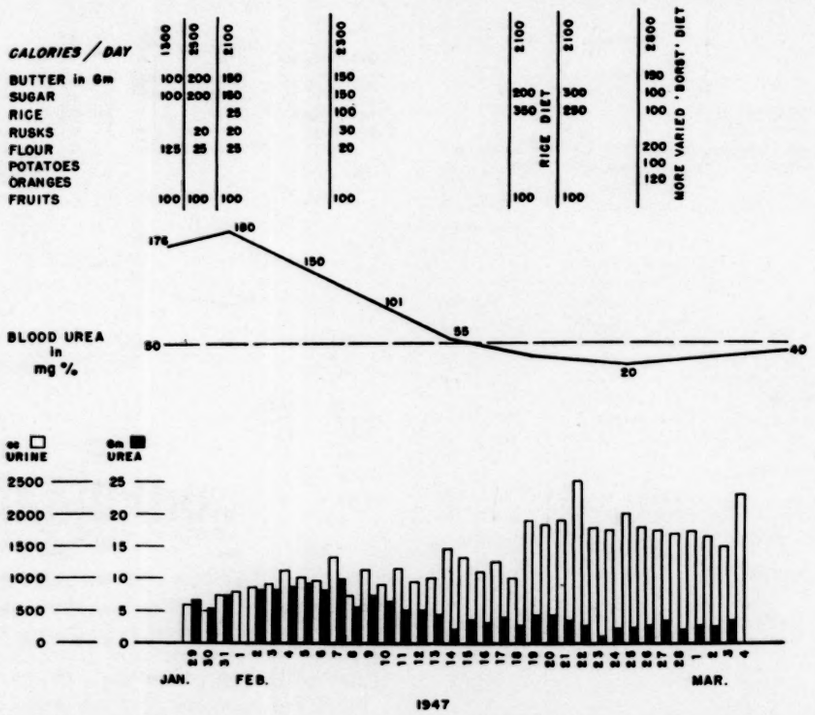

FIG. 6. A man fifty-one years of age with chronic nephritis and uremia was given a diet of 2,100 to 2,300 calories per day. His blood urea declined from 176 to 20 mg. per cent. Kempner's and Borst's diets were equally effective in reducing urea production. The daily urea excretion was only 3 gm. per day or less.

Hereinafter we will consider in detail suppression of catabolism of protein by the forced high caloric diet prescribing only 20 gm. of protein per day. Transfusion in uremia will be discussed briefly and an example of treatment with dialysis will be presented.

Forced High Caloric, Low Protein Diet. Advocates of a higher protein diet in the treatment of chronic uremia claim that a blood urea of 300 mg. per 100 ml. does not endanger the patient's life; it does, in fact, facilitate urea filtration. Nature probably was as justified in establishing the blood urea of man at 20 to 50 mg. per 100 ml. as it was in regulating the blood urea of the shark at 2,000 mg. per 100 ml. It seems reasonable, therefore, to assume that there may be some advantage in maintaining a patient in a normal range of blood urea if this is possible. It is difficult to find objective criteria

by which to judge the value of the forced high caloric diet in a group of patients who, as indicated by the nature of their disease, are certain to die within the next few years. I have tried the forced high caloric low protein diet in many patients. Some have lived with a fraction of kidney function for two or three years and seemed happier than before and in better clinical condition.

The course of a man fifty-one years old, with chronic nephritis and hypertension, is presented. (Fig. 6.) After an experimental diet he was able to ingest 150 gm. of butter, 150 gm. of sugar and 100 gm. of rice. When discharged, he took a mixture of Borst's and Kempner's diets. His condition improved remarkably.

In 1945 Kempner[14] stated that with the reduced protein and high carbohydrate intake of his rice diet the total nitrogen excretion in the urine decreased to a level considerably lower than found during complete fasting. After several weeks it decreased to 1.1 gm. of urea nitrogen per twenty-four hours.* The value of the Kempner diet in the treatment of hypertension is not discussed here but we have frequently been able to confirm its protein-sparing effect. Recently Peschel and Peschel,[27] Dole et al.[8] and Corcoran, Taylor and Page[6] reconfirmed it. Watkin et al.,[33] recognizing the fact that some nitrogen is lost with feces and sweat, believe that true nitrogen equilibrium is infrequently achieved on the unmodified rice diet. The nitrogen loss is small, however.

Figure 7 represents the course of a woman with hypertension and slight uremia following three toxemias of pregnancy. During the eight days in which she took 800 gm. of rice and 300 gm. of sugar, her blood urea fell to 12 mg. per 100 ml. However, as she objected to the pure rice diet, she was prescribed a diet composed of rice, potatoes, flour, fruit, butter and sugar. When her caloric requirements were met, she was allowed a little meat or fish. Her condition remained satisfactory for three years.

It is essential that the rice diet cover the patient's caloric requirements. In the case shown in Figure 8 this was not realized. As an insufficient amount of sugar was taken, lack of caloric intake resulted in increased urea excretion. The determination of urea excretion per twenty-four hours constitutes a reliable check of the effect of the diet and is the best indication of whether or not the patient is taking the diet.

To live on butter and sugar alone is an impossibility. Borst has worked out a diet that also contains flour and potatoes. The rice diet, even when providing sufficient calories, is not enjoyed by the majority of patients. A special bread (noury bread*) was developed in Holland for the treatment of chronic uremia. This bread contains only 2.2 per cent protein while regular bread has 7.3 per cent. Figure 9 illustrates that this bread has the same protein-sparing effect as the Borst and rice diets.

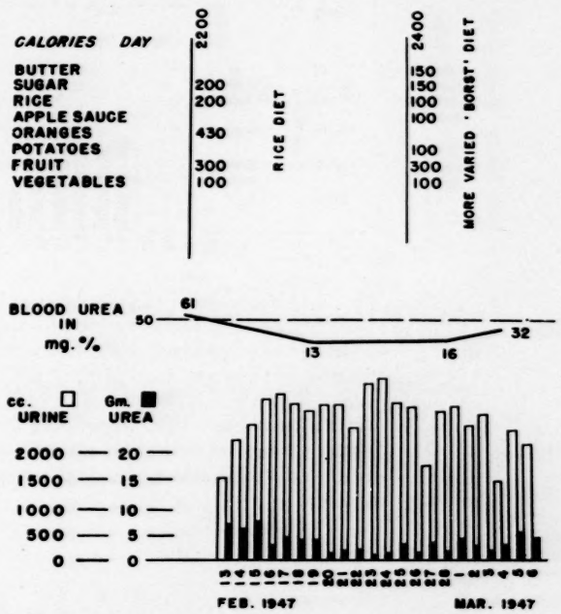

FIG. 7. A woman, thirty-two years of age, with hypertension and uremia was treated with Kempner's rice diet and later with a combination of rice diet with Borst regimen. Note how the urea excretion was reduced ½ to 3 gm. per twenty-four hours.

A man thirty-six years old, with nephrocalcinosis and uremia without hypertension was first given butter and sugar and was later prescribed 200 gm. of butter and 300 gm. of noury bread per day. During this period his urea excretion was only 2 to 3 gm. per twenty-four hours.

Using low protein bread, rice, butter, sugar, potatoes, vegetables and fruits, it is possible to offer a reasonable diet containing only 20 gm. of protein per day. While it has been generally accepted that at least 1.2 gm. of protein per kg.

* The twenty-four-hour urinary urea excretion on a 100 gm. protein diet is about 25 gm. In complete starvation 12 gm. of urea is excreted = approximately 6 gm. of urea nitrogen.

* Made by Nourypharma Deventer, Holland. Medical Division, Mr. Horbach.

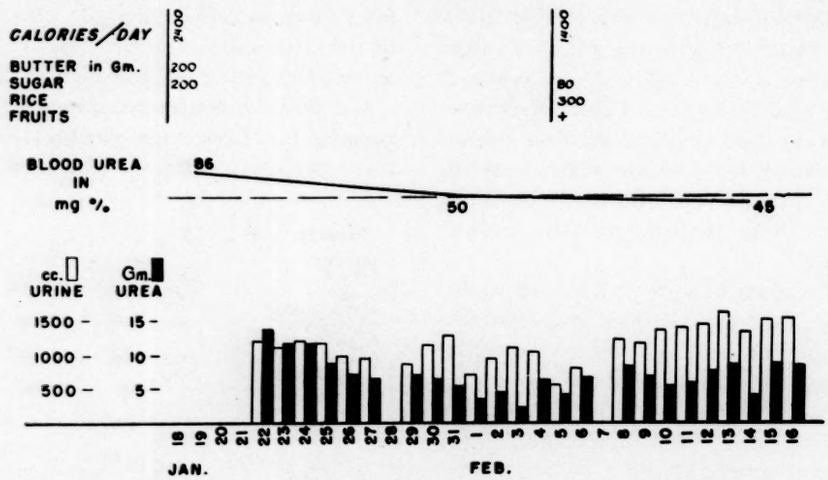

FIG. 8. A forty-five year old woman with polycystic kidneys and uremia was in poor health for a few months. She was given the butter-sugar diet in its strictest form. As was expected the urea excretion decreased to about 4 gm. per twenty-four hours; she was then given a rice diet. When the urea excretion mounted to about 8 gm. per day, it was decided that the diet was deficient. It was proved later that she had been given only 80 gm. of sugar per day instead of 200. This patient was able to lead an almost normal life when given a more extensive high caloric diet. However, she died one year later from infection in the cysts of one kidney.

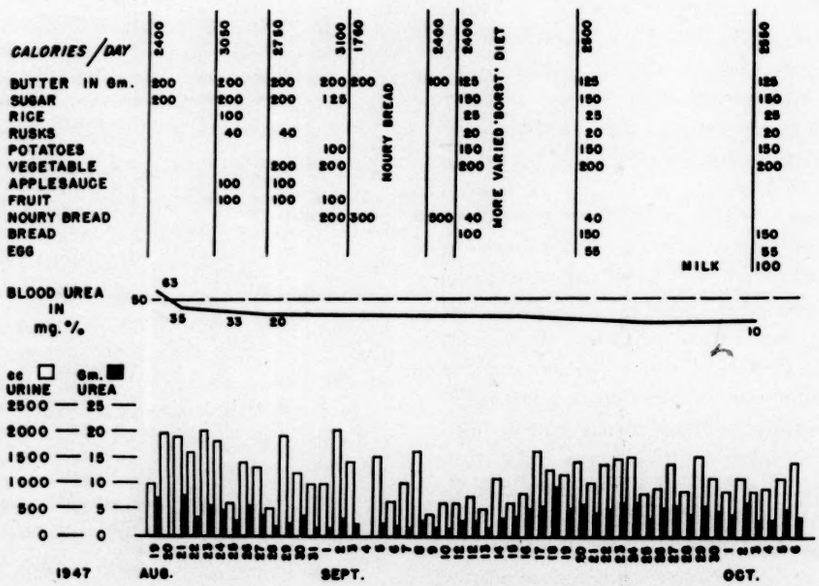

FIG. 9. A man of thirty-six with nephrocalcinosis was given the butter and sugar diet for a few days; the urea excretion was low, then noury bread and butter were given; the urea excretion stayed at the same low level. When his caloric requirement was covered, it was possible to expand the diet with 150 gm. of normal bread, one egg and 100 gm. of milk. His blood urea remained low.

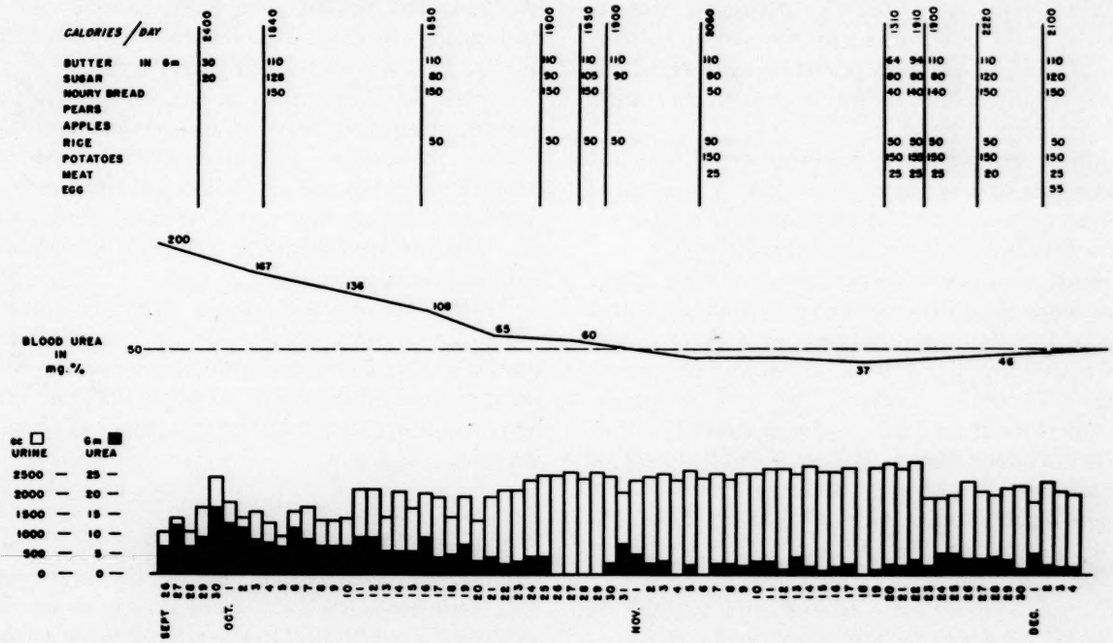

FIG. 10. A man of sixty-three with large polycystic kidneys and uremia remained well for two years on a forced high caloric diet. When his blood urea was low, meat and eggs were allowed; his caloric requirements were well covered all the time.

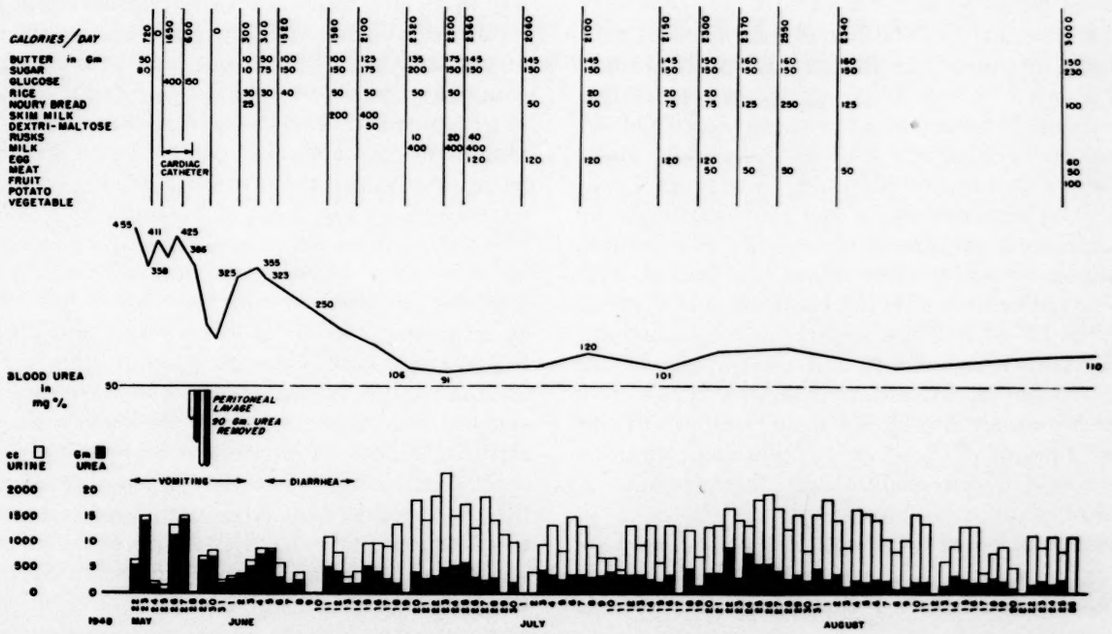

FIG. 11. A twenty-five year old teacher had chronic nephritis, uremia and hypertension. She was admitted with a blood urea of 455 mg. per cent. A diet was tried but constant vomiting made the suggested regimen impossible. The vomiting persisted after four days of treatment with 40 per cent glucose through a catheter. Thereafter she was treated with peritoneal lavage. The blood urea was reduced from 368 to 172 mg. per 100 ml. It rose again but vomiting stopped and she was able to take more of the butter and sugar diet. She could ingest large amounts of calories by using baked potatoes or low protein bread with butter. Upon discharge she had a blood urea of about 100 mg. per 100 ml. and a urea excretion of 3 to 4 gm. per day. She returned to her profession and lived for one and a half years although blood transfusions had to be given intermittently. She died after pericarditis developed.

of body weight is required to maintain protein balance, Borst, Kempner and the writer believe that 20 gm. of protein per day suffices if the caloric requirements of the body are met with carbohydrates and fat.

A high caloric diet containing 20 gm. of protein per day may not deplete the body proteins and does not reduce the concentration of serum proteins.* (Borst and Kempner.)

Figure 10 shows the course of a man sixty-three years old with large polycystic kidneys and uremia but without hypertension. His blood urea of 200 mg. per 100 ml. gradually decreased and, on becoming normal, the urea excretion was not more than 3 gm. and occasionally 5 gm. per twenty-four hours. It was possible to allow 150 gm. of meat and a half egg per day. He needed large supplements of vitamin B to control a sore tongue. He has been in fair condition for over two years.

The protein content of the diet should be increased as soon as the blood urea is about normal. If the patient enters an anabolic phase in which protein is used for cellular reconstruction, a positive nitrogen balance may be possible.

Blood Transfusion. We have often observed an improvement of the hemoglobin during this dietary treatment, as in the patients reported in Figures 7, 8 and 9. We prefer to restrict the less valuable proteins and to allow 50 gm. of meat, one egg or 100 gm. of milk, which may make the diet more palatable. Sometimes, however, the hemoglobin is low and continues to decline, as in patients with chronic uremia and malignant hypertension. Borst has shown, and I have confirmed, that the transfusion of 500 ml. of fresh blood will not appreciably increase the urea excretion and will not elevate the blood urea. Although 100 gm. of protein administered in this manner is used for tissue anabolism, the same amount of blood or an equivalent amount of protein given orally leads to excretion of 20 gm. of urea.

Treatment with Dialysis, Artificial Kidney or Peritoneal Lavage. In severe uremia in which vomiting and general distress of the patient prohibits the intake of a high caloric diet, a preliminary dialysis may improve the condition so that he may be able to take his diet.

Figure 11 shows that a patient with severe chronic uremia is never in too serious condition to try treatment. This twenty-five year old woman with severe uremia was treated with peritoneal lavage and was able to return to work as a teacher after being placed on a forced high caloric low protein diet.

As the low protein noury bread is not yet available in the United States, a few other suggestions using foods available in this country have been given in the section on acute uremia. They are even more useful in the treatment of chronic uremia.

SUMMARY

Many of the symptoms of so-called acute uremia are due to overloading the body with salt and fluids. Water restriction and salt deprivation are essential in the treatment of anuria. It is shown that catabolism of the body proteins and urea production can be greatly reduced if the patient's caloric requirements are met with carbohydrates and fat. It is emphasized that the patient should not be allowed to eat as little as he wants but that he should be persuaded or even forced to take the high caloric diet (Borst), hence the term forced high caloric diet. It is demonstrated in several of the cases reported herein that urea excretion (and production) can be reduced to 2 to 5 gm. per twenty-four hours. The patient's serum potassium may be lowered by this diet. Severe intoxication, infections, crushing injuries or necrosis may, however, cause a rapid rise in blood urea and potassium.

Some patients were first seen after severe uremia and overhydration had already developed. In those patients dialysis with the artificial kidney or peritoneal dialysis improved their condition so that they were able to take the high caloric diet. Although there is no need to give protein to a patient with acute uremia so long as his caloric requirements are covered, the patient with chronic uremia should be given approximately 20 gm. of protein per day. This is well under the limit of 40 gm. generally advocated in this country, except by Kempner. With rice, butter, sugar, ice cream, potatoes, vegetables and fruits a satisfactory diet is possible. Some suggestions for the diet have been presented. It is the author's impression that patients with chronic, severely impaired kidney function

* Whether the high fat content of the Borst regimen will increase the lipoprotein in the blood serum (now suspected of causing arteriosclerosis) will have to be studied. These patients do not live long and it is questionable how harmful the fat would be in a relatively short period. It is difficult to prescribe a diet high in calories when not only the protein but also the fats have been reduced. Kempner's diet is an example.

may live longer and more comfortably when using this diet.

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Treatment of Peripheral Arterial Obliterative Diseases and Their Complications by Arterial Infusions of Histamine*

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THE technic and success of intra-arterial infusions of histamine for obliterative peripheral arterial diseases have been described recently[7,8] in small groups of patients. The present report deals with the results of this form of therapy in 133 patients with this disorder. The obliterative arterial disease in these cases was variously due to thrombo-angiitis, arteriosclerosis and arteriosclerosis with diabetes and embolism.

PATIENT MATERIAL

The first group consisted of 107 patients with impalpable popliteal artery pulsations. Since a normal popliteal artery is often not easily palpated, its absence was always definitely established by a very low or absent oscillometric reading in the upper half of the leg. These readings are recorded in Table I.

A second group was comprised of ten patients who had no palpable femoral artery in the inguinal region but who, despite this, were able to receive a series of femoral artery infusions. Their oscillometric readings in the upper half of the leg were zero to a mere flicker. (Table IV.) Many in these two groups had neural and orthopedic disorders. Some had superficial necrosis and infections but none had frank gangrene or deep infections.

The third group of sixteen patients had severe infections complicating their advanced peripheral vascular disease. The character and extent of these infections are listed in Table V together with oscillometric readings.

Treatment. The infusions of histamine were given in a manner similar to that described previously[8] with one modification: the sphygmomanometer was found to be superfluous. A 500 cc. flask or bottle is capped with a two-hole stopper. Through one opening a piece of glass tubing reaches above the solution while the outer end connects with an air filter and a blood pressure bulb. From the other opening in the stopper the solution is permitted to escape through a drip indicator and thence through narrow tubing into a Kaufman syringe. A prepared infusion set, such as the Venopak, can be adapted for use in a similar manner although not as satisfactorily. The skin and the subcutaneous tissue over the artery are infiltrated with 5 cc. of a 2 per cent solution of procaine, with avoidance of the femoral nerve. The infusion needle should be short bevelled 20 gauge, 1½ inches long; for the very stout patient 2 inches long. The needle is inserted cephalad into the femoral artery. The pressure in the bottle is then raised until the pulsating blood can be seen in the syringe only during each systole. If the blood pressure in the femoral artery is low, this will not occur and suction must be created by pulling up the piston.

The basic solution employed consists of 500 cc. of normal saline to which is added as much as 2.75 mg. of histamine phosphate. It was found that between two and five drops per heart beat permits an erythema of the thigh to develop with few or no subjective symptoms. Flushing of the face without headache is of little importance. An infusion ideally brings about a marked erythema from groin to tips of toes, increases skin temperature and causes filling of the superficial veins. The infusion is given weekly and if the symptoms are totally disabling, semiweekly. A set of instructions on foot hygiene is given to each patient.

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For the patient with severe infection the bottle is prepared in the same manner but, in addition to histamine, aureomycin hydrochloride buffered with sodium glycinate and crystalline penicillin are added to the solution. No local damage, vascular or extravascular, has ever occurred during an infusion although given as often as six times weekly when necessary. There is no local pain during or after an infusion as long as the needle tip remains in the lumen of the artery. The frequency of these infusions and the dosage of the antibiotics were varied with the intensity of the infection. Crystalline penicillin can be used in unlimited quantities, with an

TABLE I

EFFECT OF HISTAMINE ON THE WALKING TOLERANCE OF PATIENTS WITHOUT POPLITEAL PULSES

Case No.	Diagnosis	Oscillometric Readings of Leg		Walking Tolerance in Blocks		No. of Treatments Required
		Upper Half	Lower Half	Before Treatment	After Treatment	
1	AS	1.5	1.0	1	15	10
2	ASD	1.0	0.7	1	15	9
3	AS	1.0	1.0	2	10	5
4	AS	0.5	0.1	1	7	10
5	AS	1.0	0.5	2	15	8
6	AS	1.0	0.8	.5	8	7
7	AS	2.0	1.0	2	8	5
8	AS	1.0	0.1	1	5	3
9	ASD	1.0	0.5	.5	6	5
10	AS	0.5	0.1	.5	4	6
11	ASD	0.8	0.2	1	8	6
12	E	0.0	0.0	0	5	7
13	AS	0.0	0.0	1	1	5
14	AS	0.5	0.1	-.5	10	9
15	AS	1.0	1.0	1	8	8
16	AS	0.1	0	2	7	9
17	AS	0	0	-1	3	8
18	AS	0.1	0	.5	5	7
19	AS	1.0	0.2	2	10	8
20	AS	0.5	0	2	15	7
21	ASD	0.5	0.1	.5	6	9
22	AS	0.5	0.2	2	2	6
23	ASD	1.0	1.0	0	4	7
24	AS	0.2	0	1	9	5
25	AS	0	0	1	6	5
26	ASD	0.6	0	-.5	2	9
27	AS	0	0	-.5	4	10
28	AS	2.0	0.5	1	9	10
29	ASD	0	0	.5	5	7
30	AS	0.1	0	.5	4	6
31	TAO	0.2	0	0	15	8
32	ASD	0.5	0	.5	6	10
33	AS	1.0	0.5	2	15	7
34	AS	1.0	0.8	4	15	7
35	AS	0.5	0	1	12	3
36	AS	0.5	0	.5	15	7
37	AS	0.15	0.2	2	6	7
38	AS	0.5	0.5	3	15	4
39	AS	0.1	0	2	9	6
40	AS	1.5	1.2	2	6	8
41	TAO	1.2	0.5	1	8	4
42	AS	0.5	0	1	8	4
43	ASD	0.2	0	-.5	5	6
44	TAO	0.5	0.5	-.5	2.5	6
45	AS	0.5	0	.5	15	8
46	AS	0	0	-.5	4	6
47	AS	0.5	0	2	8	10
48	TAO	2.0	1.5	2	15	4
49	AS	0.7	0	1	5	6
50	AS	0	0	2	2	6
51	TAO	0.8	0.2	.5	7	8
52	AS	0.5	0.2	2	11	6
53	ASD	0	0	2	2	6
54	AS	0.7	0	3	15	6
55	AS	0.5	0	.5	1	6
56	AS	1.5	1.0	2	7	10
57	AS	0.3	0	-1	3	8
58	AS	1.2	0	1	4	6
59	AS	0.5	0.5	2	2	6
60	AS	1.0	0.2	.5	6	5
61	AS	0.5	0	2	4	5
62	AS	0	0	-1	8	7
63	AS	0.2	0	1	15	12
64	AS	0	0	1	8	5
65	AS	1.0	1.0	1	6	6
66	TAO	2.0	1.0	3	10	3
67	AS	0.5	0.2	2	11	6
68	TAO	0.5	0.2	.5	4	6
69	ASD	0.2	0	.5	10	6
70	AS	0	0	1	8	7
71	AS	0	0	2	2	6
72	AS	0.5	0.2	.5	8	4
73	AS	0.1	0	1	5	6
74	AS	0.3	0	1	15	7
75	AS	0.2	0.1	2	10	5
76	AS	0.2	0.2	1	1	6
77	AS	0.5	0.2	2	6	7
78	AS	0.7	0.5	.5	8	10
79	AS	0	0	2	10	7
80	AS	0	0	.5	8	7
81	AS	0	0	2	10	7
82	AS	0.2	0	2	5	7
83	AS	0	0	-.5	4	6
84	AS	0.2	0	.25	6	6
85	AS	0.5	0	1	8	7
86	ASD	0.5	0	2	5	11
87	AS	0.5	0	1	20	10
88	AS	1.0	0	2	3	10
89	AS	0	0	2	13	6
90	AS	0	0	1	8	10
91	AS	1.0	0	.5	2	10
92	AS	0	0	2	7	7
93	AS	0.5	0.2	1	10	3
94	AS	0	0	.5	6	8
95	AS	0.5	0	1	6	8
96	AS	1.5	0	.5	15	7
97	TAO	1.0	0.5	1	8	10
98	AS	1.0	0.5	1	7	5
99	AS	0	0	1	6	10
100	AS	0.5	0	1	8	3
101	AS	0.8	0.5	1	1	6
102	AS	0	0	1	8	5
103	AS	0.5	0	2	8	7
104	AS	0	0	2	2	6
105	AS	0.5	0	.5	15	6
106	ASD	0.8	0	1	9	10
107	AS	1.0	0.2	1	5	6

AS = arteriosclerosis

ASD = arteriosclerosis with diabetes

E = embolism

TAO = thrombo-angiitis obliterans

awareness of its allergic properties. Aureomycin hydrochloride, buffered with glycinate, was used in concentrations of 1 mg. to 1 cc. normal saline or 5 per cent dextrose in distilled water solutions. As much as 500 mg. aureomycin has been given in each infusion. No allergic reaction has occurred to the present time. If facilities are available, a better choice of antibiotics can be made by testing for sensitivity to antibiotics of the organisms cultured from the infected areas. Expansion of the infected tissues by the hyperemia induced by histamine can cause enough pain to force discontinuance of the infusion. This interruption, however, is avoidable if the regional nerve supply is blocked with procaine at a safe distance from the infected area. The sciatic nerve in the upper angle of the popliteal space, the tibial nerve alongside the popliteal artery and the peroneal nerve as it crosses the upper neck of the fibula were infiltrated most frequently. Rarely was the posterior tibial nerve utilized. Local surgical therapy of the infected and gangrenous parts was carried out. No other form of therapy was used concurrently. Smoking was permitted to all except those who showed or gave a history of phlebitis characteristic of thrombo-angiitis obliterans. All patients were ambulatory except those who had complicating infections.

TABLE II

GRADING OF RESULTS OF TREATMENT*

Etiology	Response		
	Very Good	Good	Failure
Arteriosclerosis	46	30	10
Arteriosclerosis with diabetes	5	5	2
Thromboangiitis	6	2	
Embolism		1	
	57 (53%)	38 (36%)	12 (11%)

*Analysis of effects in 107 patients without popliteal pulses who received histamine as recorded in Table I.

RESULTS

Evaluation of the therapeutic effects of histamine infusions into the femoral artery in the patients in groups one and two is based on its influence on walking and sleep tolerances. The quantitative effect on walking ability is recorded in Table I. It will be observed that the responses are variable, and are graded as follows: Failure (F)—no increase in distance and little or no lessening in the intensity and duration of pain following a minimum of six to ten infusions; Good (G)—walking tolerance increased three or four times the original distance or up to six blocks; Very Good (VG)—walking tolerance increased to from seven blocks to unlimited distances. These criteria are obviously arbitrary. Our emphasis has always been on the actual quantitative changes in walking and sleep tolerance as tabulated in Table I. For this reason recording the patient's walking tolerance at every visit was considered most important. The patient's proneness to exaggeration, forgetfulness, the character of his neighborhood, the grade of the street, the rate of walking, his desire to please or his anxiety over the future maintenance of his improvement when treatment was terminated always required careful evaluation.

The response in walking tolerance of 107 patients without popliteal pulses (Group 1) when analyzed according to these criteria showed a failure rate of 11 per cent, a good response in 36 per cent and a very good result in 53 per cent. (Table II.) Only twelve of the patients treated in this group had diabetes and they appeared in the "good response" column rather than in the "very good" group.

In Group 2 there were ten patients who had no femoral pulsation. The response of their limited walking tolerances to histamine infusions into the femoral artery is recorded in Table IV. The results in seven cases are classified as good and in three as failures.

In Group 1 there were twenty-eight patients and in Group 2 six patients who could not sleep the night through. (Table III.) The level position of their legs in bed caused severe pain and forced them to sleep in a sitting position, feet on floor, to get some measure of relief. All these patients, except one in Group 2, were completely relieved of this night pain and were enabled to sleep in bed all night after a brief course of treatment. The exception was a patient with severe pain in one foot who had severe edema due to chronic cardiac failure, poorly controlled by mercuhydrin given three times weekly.

An example from Groups 1 and 2 will be cited.

CASE I. A physician with an embolism to the popliteal artery, arising from a mural thrombus over a fresh myocardial infarct, suffered severe pain day and night which could be relieved only temporarily by morphine. He

received etamon, papaverine, priscoline, nicotinic acid and bed rest with no avail. When his toes began to discolor and show hemorrhagic blebs, he was referred for histamine therapy four weeks after the embolization. Two infusions of histamine into his femoral artery

TABLE III

NUMBER OF INTRA-ARTERIAL INFUSIONS OF HISTAMINE REQUIRED TO ABOLISH "NIGHT PAIN"*

Case No.	Sleep Tolerance before Treatments (hr.)	No. of Treatments Required for Complete Relief
1	2	6
2	2	3
3	1	4
4	.5	3
5	2	6
6	1	5
7	2	6
8	2	7
9	1	6
10	1	4
11	0	5
12	2	5
13	3	4
14	2	3
15	2	5
16	.5	3
17	1	5
18	.5	2
19	2	4
20	2	5
21	.5	3
22	.5	6
23	1	5
24	1	5
25	4	2
26	1	4
27	.5	6
28	2	3
29	0	6
30	0	6
31	0	6
32	0	Failure
33	.5	3
34	1	5

*This pain was caused by obliterative disease of the popliteal and femoral arteries.

relieved his pain and morphine was no longer necessary. He left the hospital after his fifth infusion, able to walk three blocks.

CASE II. A patient with arteriosclerotic endarteritis of the femoral artery had had a bilateral sympathectomy performed about three months before admission to the clinic because of severe night pain and absent walking tolerance. This operation, although technically successful, failed to relieve his night pain. He received four intra-arterial infusions of histamine with complete relief of the night pain and after his sixth infusion he reported that his walking tolerance had risen from a few yards to three city blocks.

Complicating superficial cutaneous infections and wounds often disappear after histamine infusions. However, deep seated infections, with or without gangrene complicating peripheral arterial disease, cannot be handled in this manner. Sixteen such patients were treated by

TABLE IV

EFFECT OF HISTAMINE INFUSIONS INTO THE FEMORAL ARTERY ON WALKING TOLERANCE*

Case No.	Diagnosis	Oscillometric Readings of Leg		Blocks		No. of Treatments Given
		Upper Half	Lower Half	Before Treatment	After Treatment	
1	AS	0	0	0	3	9
2	AS	0	0	0	1	10
3	AS	0	0	-1	2.5	8
4	AS	0.5	0	.5	6	12
5	AS	0	0	0	4	11
6	AS	0	0	0	0	10
7	AS	0	0	0	4	8
8	AS	0	0	0	8	12
9	AS	0	0	.5	.5	10
10	AS	0	0	1	7	10

*This includes patients without femoral pulsations (inguinal).

histamine infusions containing aureomycin, penicillin, or both, as described in the section on treatment. Under this regimen, infection cleared, gangrene was delimited and pain was abolished in thirteen patients. (Table v.) Failure, with death or major amputation, occurred in three cases. One case will be cited to illustrate the problems encountered during treatment of this type of patient and the manner in which they were met.

CASE III. The patient presented himself with severe pain in the great toe and foot when walking and while in bed. His oscillometric readings in the calf at this time were 2.0 and the popliteal pulse was barely palpable. He had a mild diabetes which required no insulin. He received three intra-arterial infusions with prompt relief of his pain. Five weeks after his discharge from the clinic he returned complaining of severe pain in his calf and foot. The great toe showed signs of impending gangrene. This time the popliteal pulse was not palpable and his oscillometric readings had fallen to 0.5 in the upper half of his leg, evidently due to extension of his old thrombus. He was admitted to the hospital. In spite of sedation and priscol into his femoral

TABLE V

THE RESPONSE OF INFECTIONS COMPLICATING SEVERE PERIPHERAL ARTERIAL OBLITERATIVE DISEASE TO ARTERIAL INFUSIONS OF HISTAMINE AND ANTIBIOTICS

Case No.	Etiology*	Oscillometric Readings of Leg		Before Treatment				Arterial† Infusions of:			Effects of Treatment			Wound Culture
		Upper Half	Lower Half	Rest Tolerance (hr.)	Infection			H	A	P	Rest Pain Abolished	Infection Cleared	Healing Complete	
					Skin	Bone	Gangrene							
1	AS	0.2	0	.5	Toe	Metatarsal phalanges	Toe - L5	+		+	Yes	Yes	Yes	Strep. viridans; B. coli
2	ASD	0	0	2	Toe	Phalanges	None	+		+	Yes	Yes	Slow	
3	ASD	0.5	0		Toe; foot	Metatarsal	Toe - RI	+	+	+		Yes	Stump healed	B. coli; B. proteus; B. pyocyaneus
4	ASD	0.5	0	.5	2 Toes; foot	Two phalanges	Toe 5; toe 1 (part)	+	+	+	Yes	Yes	Yes	Staph. aureus; B. proteus
5	ASD	0.5	0	2	Toe	Phalanges	Toe	+	+		Yes	Yes	Yes	Staph. aureus
6	ASD	0	0	.5	Heel			+		+	Yes	Yes	Yes	Staphylococcus
7	ASD	0	0	.5	Toe; foot			+	+		Yes	Yes	Yes	
8	AS	0	0	.5	2 Toes	Phalanges	2 Toes	+	+	+	Yes	Yes	Yes	Strep. hemoliticus
9	TAO	1.0	0.7	2	Toes; ankle			+	+	+	Yes	Yes	Yes	
10	AS	1.0	0.5	3	Toes; foot			+	+	+	Yes	Yes	Yes	
11	AS	1.0	0.5	.5	Toes; foot	Two toes						Amputation		B. coli; Enterococcus
12	ASD	0	0	1	Toes; leg			+	+	+	Yes	No; died		Staph. aureus; B. coli
13	ASD	1.0	0.5	4	2 Toes		2 Toes	+	+	+	Yes	Yes	Yes	
14	ASD	2.0		0	Heel; leg		Heel, foot and leg	+	+	+	Less	Slow Amputation		Staph. hemoliticus; Ps. aerogenes
15	AS	0	0	1	Leg	Tibia	Leg (13 x 7 cm.)	+	+	+	Yes		(3 x 2 cm.)	B. coli; B. pyocyaneus; Staph. aureus
16	ASD	3.0	1.0	1	Foot; tendons	Four metatarsals	Foot; 4 toes	+	+	+	Yes	Yes	Yes	Enterococcus; B. pyocyaneus

*AS = arteriosclerosis; ASD = arteriosclerosis with diabetes; TAO = thromboangiitis obliterans.
†H = histamine phosphate; A = aureomycin glycinate; P = crystalline penicillin.

artery the pain persisted. Bed rest caused so much pain that it forced him to walk about the ward all night to obtain some degree of relief. As a result edema developed in the foot. This caused the web between toes four and five to crack and a lymphangitis developed and spread steadily from toes to ankle. Surgical consultants considered the situation hopeless and believed amputation inevitable. Priscoline was discontinued because it caused precordial pain and a sense of impending death. It was decided to try daily infusions of histamine, penicillin and aureomycin. However, few of the treatments could be completed because of the intense pain caused by the vasodilatation. When peroneal nerve blocks with 2 per cent procaine at the neck of the fibula were performed before each infusion, the development of pain in his infected toes during the infusion was prevented. As soon as the full infusion could be tolerated the situation quickly reversed itself. He was able to stay in bed and sleep all night. This helped clear the edema. The lymphangitis disappeared. The gangrenous areas on the first and fifth toes became demarcated. The infusions were reduced to a semi-weekly schedule and self-amputation of the distal half of the fifth toe and the tip of the great toe took place. Two months after institution of treatment the stumps were healed and the patient walked without crutches.

COMMENTS

The results obtained in this large group of patients with uncomplicated peripheral arterial disease corroborate those reported earlier in a smaller series of cases. The patient with arterial disease of the popliteal and femoral arteries now has, with this regimen, an 85 per cent chance of increasing his walking and an almost 100 per cent chance of obtaining unlimited sleep tolerance. Two recent reports support these claims.[5,10]

The mechanism accounting for the mounting increments of improvement which follows each infusion until a peak is reached and then maintained with little or no treatment in most of the patients is a matter for speculation. In an affected leg one can assume the presence of two arterial systems. One is the *cognate system* in which an important large artery is known to be blocked partially or completely and its tributaries receive little or no blood directly. The blood pressure in such a vessel is low; when the iliac artery is partially blocked by a thrombus, we found the blood pressure in the femoral artery of three patients, as measured by a von Moritz and Tabora type venous pressure apparatus, to range between 20 and 150 mm. water, and the blood flow is correspondingly reduced. The other is the *collateral system* which consists of arteries still open and able to bring blood to the extremity from the aorta. The cognate arterial blockade is by-passed by means of inter-arterial anastomoses which bridge blood from the collateral arteries to the capillaries of the cognate system. The efficiency of the blood supply to an affected extremity will depend upon the quantitative balance struck by these two arterial systems. Clinically, the deficit is reflected in the reduced walking and sleep tolerances. Physiologically, it is made apparent by prolonged femoral A-V equilibration times which we have found to reach as high as fourteen minutes compared to a normal of less than three minutes, lowered radiosodium diffusion curves over foot and calf and prolonged circulation times from femoral artery to tongue.[6,9] Blood from the aorta therefore must traverse many devious narrow pathways to reach the capillaries before returning through the femoral vein. To be successful any form of treatment must reverse this stagnation and increase blood flow. A drug must expend itself completely or nearly so in the involved arterial system within the period of femoral A-V equilibration time. To do otherwise would permit the unused portions of the drug to escape into the systemic circulation and cause a generalized vasodilatation. The well vascularized tissues, with their labile arteries, rather than those with insufficient blood supply would receive the greater share of the fixed volume of blood.[2,6,7] The intra-arterial introduction of histamine localizes the drug where it is needed most. The effects of this powerful but short-lived vasodilator are not only maintained but progressively augmented by the slow administration of the drug in dilute solution. A maximum blood flow is thus attained. This has been confirmed by blood flow studies using radiosodium. These showed that circulation increased after intra-arterial histamine in the calves of 90 per cent of thirty patients,[9] a figure which agrees closely with our clinical results in which a good response to treatment occurred in 89 per cent of patients without popliteal pulses. Femoral A-V equilibration times were reduced and A-V oxygen differences narrowed. The prolonged duration of beneficial effects following the very temporary intensive periods of vaso-

dilatation repeatedly induced by intra-arterial infusions of histamine indicates that the collaterals are permanently enlarged by this treatment. Thoma, from his observations on collateral circulation approvingly quoted by Lewis,[3] decided that length and caliber of arteries can be increased permanently by the augmentation of blood through them. Over a long period of time this may take place spontaneously in legs when the main artery has been severed or ligated. Minimal increases in blood flow follow the hemodynamic pressure changes induced by walking or standing. Histamine accomplishes this and more in brief periods of two to ten weeks because it is the most powerful vasodilator available and its effects can be prolonged at will by the duration and frequency of administration by infusion. We have not been able to duplicate this degree of success with intra-arterial priscoline, which is not as powerful or as prolonged a vasodilator as histamine. Sympathectomy cannot produce the same degree or type of vasodilatation as histamine[9] and, although its effect is longer lasting, it is still very limited according to the studies of Lynn and Barcroft.[4] Further, the major dilatation takes place in the blood vessels of the lower abdomen which may abstract blood from a foot without collaterals.[1,2] Histamine has helped where sympathectomy has failed.

The rapid hydrolysis of histamine has an important advantage not shared by other vasodilators. If an untoward reaction should occur, stopping the infusion abruptly ends the influence of histamine. This does not occur when a drug like priscoline, with its many side effects, is used. Many arteriosclerotic patients have coronary or cerebral artery disease. If anginal pain should occur, stopping the infusion of histamine abolishes its effect on cardiac output in a few moments.

Failure of histamine to help about 15 per cent of our cases may be attributed to several causes. The collateral arterial system to begin with may be totally inadequate. Extravascular complications, when present, produced persistent vasospasm, thus placing an additional load on the collateral circulation which counterbalanced the dilating effects of histamine.[9] In this group we have encountered orthopedic derangements with severe static bone and muscle imbalance, neural complications, (motor and sensory, the result of obliteration of the nutrient arteries) neurologic diseases such as posterolateral sclerosis, arthritis and painful pyogenic and fungus infections. Edema rendered an otherwise adequate collateral system almost unavailable,[9] diminishing the effectiveness of histamine infusions. Whether the edema was due to cardiac failure, thrombophlebitis or an irreversible atony of the capillaries with erythromelalgia-like symptoms such as is seen at times in very severe endarteritis, was immaterial. Patients with thromboangiitis who do not stop smoking negate the benefits of the treatment. Some of these difficulties are preventable if prompt and vigorous care of the extravascular as well as vascular problems is instituted.

Arterial disease complicated by deep-seated infections has heretofore usually been considered hopeless. The availability of antibiotics which can be given intravenously has changed this. Crystalline penicillin has been given by many in concentrated solutions. We have tried this alone and with priscoline. It causes a sense of burning down the leg which, to the unitiated, means that vasodilatation has brought the drug to the foot but it is really a referred pain due to the local irritation of the artery by the concentrated drug. Aureomycin cannot be given in concentrated solution because of its difficult solubility and the incidence of thrombosis when given intravenously. When given daily in dilute solution into the rapid flow of the arterial stream, no local pain and no thrombosis resulted in any instance. When given intra-arterially in dilute solution over a period of thirty to forty-five minutes, the antibiotics exert their bactericidal and bacteriostatic effects in concentrations not possible by any other means. The results obtained in our Group 3 patients by a combination of vasodilators and antibiotics, with meticulous care of the devitalized tissues suggest an improvement over previously employed methods. Final evaluation of our encouraging results in these patients must be deferred, however, because of the small number treated. Variables to be considered are total blood flow, virulence of organisms, sensitivity to the antibiotics and the extent and location of tissue necrosis and infections.

CONCLUSIONS

1. The intra-arterial method for infusion of a vasodilator drug such as histamine has a physiologic basis because it localizes and enhances the action of the drug in the affected extremity.

2. This method of utilizing histamine was effective in improving walking tolerance and

abolishing night pain in patients with peripheral arterial disease. In 107 patients without a palpable popliteal pulse, the effect on walking tolerance was very good in 53 per cent, good in 38 per cent and without benefit in 11 per cent. In ten patients without a femoral pulsation the response in walking tolerance was good in seven patients and without benefit in three. Night pain was abolished in thirty-three patients without femoral or popliteal pulses and failed in only one patient.

3. Severe infection complicating peripheral arterial disease was successfully combated in a majority of the patients treated when the antibiotics, aureomycin and penicillin, were combined with histamine in almost daily infusions.

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Review

Intercapillary Glomerulosclerosis: A Clinical and Pathologic Study

*I. Specificity of the Clinical Syndrome**

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FOURTEEN years ago Kimmelstiel and Wilson[1] reported a series of eight cases that presented a peculiar type of renal lesion to which they applied the term intercapillary glomerulosclerosis. Seven of the patients were known diabetics; the last, having insufficient clinical data at the time of death, was never established as a diabetic. All of the patients had hypertension and albuminuria.

Since that time considerable controversy has arisen over the specificity not only of the histologic lesion but also over the integrity of the clinical entity. Many observers[2–6] have considered the renal lesion specific for diabetes or at least sufficiently characteristic to suspect strongly the clinical presence of diabetes. Others[7–8] have disagreed with this view. Horn and Smetana[9] stated that "although intercapillary glomerulosclerosis in its more advanced state is seen only in cases of diabetes, it is not of necessity associated with a particular clinical syndrome which includes diabetes mellitus." They found an incidence of 25.4 per cent of intercapillary glomerulosclerosis in cases of arteriolar nephrosclerosis without diabetes.

Much of the confusion has arisen on strictly morphologic grounds. The original description by Kimmelstiel and Wilson made reference to a peculiar distribution of globular pink hyaline masses about the periphery of the vascular tufts of the glomerulus. These hyaline masses were distinct in having an apparent intercapillary position, thus pushing ahead of them as they increased in size intact patent capillary loops which thus formed "halos" about these masses. Since this original description many observers and Kimmelstiel himself have come to use the term intercapillary glomerulosclerosis in a more general sense to imply any form of glomerular fibrosis found in the mesangium of the glomerular tuft. Such a general descriptive use of the term has necessarily included a great variety of degenerative lesions that affect the glomerular tuft, most particularly, nephrosclerotic and arteriosclerotic changes as well as the characteristic Kimmelstiel-Wilson lesion.

In our experience, however, it appears possible to separate these two types of intercapillary glomerulosclerosis into a non-specific diffuse variety and a distinct nodular peripheral variety which, it is our contention, remains characteristically associated with diabetes and is a pathognomonic feature of this disease entity. Such a distinction has been suggested by Kimmelstiel and Porter in their recent report.[10]

Granted that there may be cases of intercapillary glomerulosclerosis whose clinical investigation is insufficient either to establish or for that matter to rule out the diagnosis of diabetes, in our experience the presence of diabetes mellitus correlates too closely with the specific histologic findings not to consider the lesion pathognomonic. The consideration of the anatomic aspects of this problem will be taken up in a later article, the present paper concerning itself only with the problem of whether a clinical entity can be distinguished.

From the clinical standpoint much confusion exists over the question of the diagnostic specificity of this syndrome. The earlier papers[2,3,5,11–13] suggested a definite clinically recognizable syndrome. Others[4,7–9,14,15] questioned the existence of clinical characteristics sufficiently constant

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to warrant establishing a clinical diagnosis. More recently Rifkin et al.[16] and Mann, Gardner and Root[17] have expressed the opinion that a distinct clinical picture is associated with intercapillary glomerulosclerosis.

It is not widely appreciated that the original description referred only to a specific pathologic entity to which a more or less characteristic group of clinical features was attached. Hence from the outset the Kimmelstiel-Wilson syndrome has not been a sharply defined clinical entity. The fact that this original description contained one case in which the diagnosis of diabetes was not established has given rise to the belief that diabetes mellitus is an inconstant feature. Moreover, hypertension and albuminuria are such common characteristics of patients of advanced age that these findings are of little diagnostic or differential significance. Thus the clinical entity has remained poorly delineated to the present time.

This clinical problem has been attacked by two methods. In this article a large group of diabetic patients were evaluated from the clinical standpoint alone. Specifically it was desired to attempt to select on purely clinical grounds out of a group of known diabetics those patients who would show the lesion of intercapillary glomerulosclerosis at autopsy. No non-diabetic cases were reviewed because, in our opinion, in the absence of this clinical finding no syndrome of intercapillary glomerulosclerosis can be said to exist. It was thus hoped to put to critical test any so-called diagnostic or pathognomonic criteria or symptom complexes. These results were then correlated with the postmortem findings and the diagnostic validity of the various features evaluated.

In a separate report to follow 100 established cases of this lesion have been analyzed clinically. In order to highlight the diagnostic worth of the various clinical features comparisons were made with a large group of diabetic patients known not to have intercapillary glomerulosclerosis.[18]

METHODS

The clinical records of patients with diabetes mellitus autopsied at the Mallory Institute of Pathology at the Boston City Hospital during the years 1934 to 1946 were reviewed. At the time of the review the anatomic diagnoses were completely unknown to one of us (J. R.). Excluding those cases in which insufficient clinical data were available for adequate evaluation, 229 were suitable for study.

The criteria established for selecting the cases of intercapillary glomerulosclerosis were based on the more or less accepted features of albuminuria, hypertension, edema and diabetes. Diabetes was considered to be present if a fasting blood sugar had been 140 or over and some glycosuria had been present. They were then separated into "probable" and "possible" categories based on the following clinical standards. (Table 1.)

TABLE 1
CLINICAL FINDINGS REQUIRED FOR "PROBABLE" DIAGNOSIS OF INTERCAPILLARY GLOMERULAR SCLEROSIS

Albuminuria	Hypertension	Edema
2–4+	Minimal to marked	Generalized
3–4+	Minimal to marked	Dependent
Clinical Findings Required for "Possible" Diagnosis of Intercapillary Glomerular Sclerosis		
3+	Moderate to marked	None
4+	Minimal to marked	None

Although numerous instances of intercapillary glomerulosclerosis are reported in which albuminuria is absent or present in only 1 or 2 plus amount, the majority of cases reported have had at least 3 or 4 plus albuminuria. Moreover, previous clinical experience has led us to the belief that of the classic triad, next to diabetes albuminuria is the most significant diagnostic finding in the Kimmelstiel-Wilson syndrome. Hence 3 to 4 plus albuminuria was demanded as a requisite for the diagnosis to be "probable." It was moreover decided that accompanying this albuminuria there must be some edema and some hypertension. When a generalized nephrotic type edema was present, a 2 plus albuminuria was considered adequate. Hypertension was divided into three grades of severity as follows: minimal when the systolic pressure ranged from 140 to 170 mm. and the diastolic was 90 mm.; moderate when the systolic pressure ranged from 140 to 190 mm. and the diastolic 90 to 115 mm.; and marked when the systolic pressure was 190 mm. or higher and the diastolic 115 mm. or higher. Hypertension was, in our opinion, the most variable and least significant as a diagnostic aid. The age group

of patients under consideration is more than likely to have varying degrees of hypertension totally unrelated to any specific renal lesion.

In the absence of edema but with the previously cited 3 to 4 plus albuminuria two sets of criteria were established for those cases in which the diagnosis was listed as "possible." Essentially those patients with higher degrees of albumin in the urine were required to have less marked hypertension.

TABLE II

Results in Cases Listed as "Probable"

Clinical Findings:

Albuminuria	Hypertension	Edema	No. of Cases	No. Correct	No. Incorrect	Per cent Error
2–4+	Minimal to marked	Generalized	4	3	1	
3–4+	Minimal to marked	Dependent	22	17	5	
Total			26	20	6	24

Results in Cases Listed as "Possible"

Clinical Findings:

Albuminuria	Hypertension	Edema	No. of Cases	No. Correct	No. Incorrect	Per cent Error
3+	Moderate to marked	None	6	2	4	
4+	Minimal to moderate	None	9	6	3	
Total			15	8	7	47

RESULTS

Using these criteria on the clinical records of the 229 cases of diabetes the diagnosis of intercapillary glomerulosclerosis was considered probable in twenty-six cases and possible in fifteen cases, a total of forty-one cases. After the selection had been made on clinical grounds alone, the autopsy protocols and microscopic sections listed as intercapillary glomerulosclerosis were reviewed and the clinical results correlated with the autopsy findings to evaluate our diagnostic accuracy.

Of the twenty-six cases considered as probable instances of intercapillary glomerulosclerosis twenty were subsequently shown to have anatomic lesions. The remaining six cases proved not to have intercapillary glomerulosclerosis. Five of these six cases had 3 to 4 plus albuminuria, minimal to marked hypertension and dependent edema. The remaining case had generalized edema and only 2 plus albuminuria.

In the whole group of 229 cases of diabetes mellitus the pathologic records revealed that sixty-six had a specific lesion diagnosed as nodular intercapillary glomerulosclerosis; yet clinically only twenty cases were considered as probably having the syndrome and an additional eight as possibly belonging in this category. In other words, a total of only twenty-eight cases of a possible sixty-six were correctly selected on the basis of having diabetes mellitus, at least 3 to 4 plus albuminuria, some edema usually of the dependent type and some hypertension. It is apparent that thirty-eight of the anatomically established cases did not present these findings. The results are summarized in Table II.

COMMENTS

Of the twenty-six cases considered as probable instances of intercapillary glomerulosclerosis only twenty proved to have this lesion, a false positive error of 24 per cent. In the less well defined "possible" category seven of the fifteen selected cases proved not to have anatomic lesions, an error of 47 per cent.

Taken together, thirteen cases later proven not to have intercapillary glomerulosclerosis appeared to present clinical findings indicative of this entity, an over-all false positive error of 32 per cent. It is of interest to note that the slight relaxation of the clinical requisites between the "possible" and "probable" groups increased the diagnostic error from 24 to 47 per cent. This specifically refers to the dropping of the requisite, "edema."

From the other viewpoint thirty-eight anatomically proven cases were not correctly identified in the clinical review. These cases represent 57 per cent of the total number of instances of intercapillary glomerulosclerosis. It is worthy of note that the 57 per cent error of cases not identified as intercapillary glomerulosclerosis is significantly higher than the 32 per cent error of those cases incorrectly called intercapillary glomerulosclerosis. This suggests that the syndrome may be more frequently missed than misdiagnosed.

It is, of course, obvious from the aforementioned results that no well defined clinical syndrome of intercapillary glomerulosclerosis exists even in the required presence of diabetes mellitus. The associated findings of albuminuria,

edema and hypertension in an older age group of patients proven to have vascular degenerative disease produce no distinctive pattern permitting accurate clinical selection.

The so-called nephrotic picture was encountered only four times and in one instance the patient subsequently proved not to have intercapillary glomerulosclerosis.

CONCLUSIONS

The clinical records of 229 diabetics were evaluated on strictly clinical grounds as to the "possible" or "probable" presence of intercapillary glomerulosclerosis. The clinical diagnoses were then correlated with the autopsy records. Of the forty-one cases selected clinically as having intercapillary glomerulosclerosis only twenty-eight proved to have the anatomic lesion, a false positive error of 32 per cent. Thirty-eight anatomic instances of the lesion were not selected because no apparent diagnostic clinical features were present; hence of a possible sixty-six cases only 43 per cent (twenty-eight) were correctly identified. No clear-cut clinical syndrome, even in the presence of diabetes mellitus, can be said to exist and a diabetic not having this anatomic lesion may present the so-called classic features of intercapillary glomerulosclerosis.

An analysis of a large series of proven cases of intercapillary glomerulosclerosis, to be presented in Part II, is needed to ascertain which of the so-called classic clinical features has the greatest differential significance and to determine whether any additional clinical findings have value in more clearly defining this entity clinically.

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Intercapillary Glomerulosclerosis: A Clinical and Pathologic Study

*II. A Clinical Study of 100 Anatomically Proven Cases**

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IN view of the conclusion presented in Part I of this paper, namely, that a clearly defined clinical syndrome could not be accurately associated with the anatomic lesion of intercapillary glomerulosclerosis, the clinical features of a series of 100 diabetic patients with proven intercapillary glomerulosclerosis were compared with a group of 176 diabetics without intercapillary glomerulosclerosis. The clinical features compared included age, sex, duration of diabetes, severity of diabetes, hypertension, edema, albuminuria, azotemia and cardiac failure. The anatomic causes of death of this series of patients with intercapillary glomerulosclerosis were compared with a control group of diabetic patients. It was reasoned that in a large series of patients with diabetes those having intercapillary glomerulosclerosis might as a group demonstrate certain clinical features having some differential worth. In the individual patient our experience has indicated that the antemortem diagnosis is inaccurate.

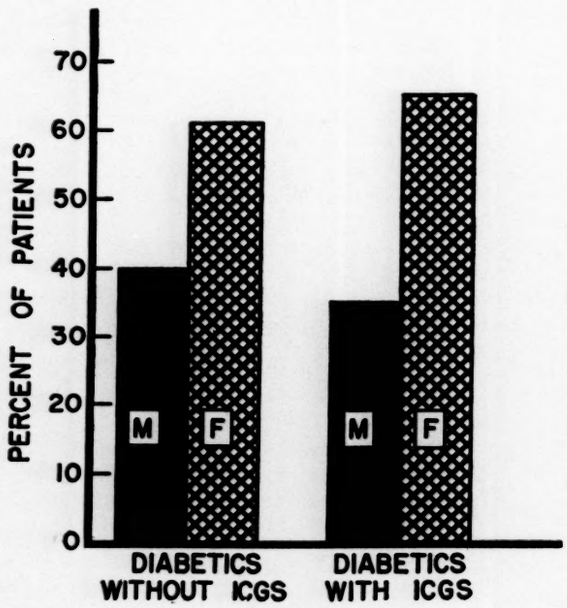

FIG. 1. Sex distribution.

Sex and Age. Figure 1 shows no essential difference in sex distribution between those individuals with intercapillary glomerulosclerosis and those without the lesion; 60.8 per cent of the diabetic patients without intercapillary glomerulosclerosis were females. It appears that intercapillary glomerulosclerosis is somewhat more common in women. This observation is in keeping with the well known greater frequency of diabetes in women beyond middle age.

The average age of the patients with intercapillary glomerulosclerosis is slightly higher than that of diabetics without intercapillary glomerulosclerosis. This difference is probably of no significance. (Table I.) In this series, which does not include child diabetics, intercapillary glomerulosclerosis is rare under fifty years of age, is most common between the ages of fifty to seventy-nine and may occur after eighty. This age distribution agrees with the findings of most other workers. Mann, Gardner and Root[2] however, hold that the syndrome is not found frequently in patients over forty years of age. This discrepancy may well be a reflection that the latter authors are reporting from a specialized service and dealing with a large number of younger diabetics. It is perhaps significant that their seven cases autopsied had had diabetes for an average of nineteen years

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prior to death, suggesting that the diabetic age rather than the chronologic age is the important factor.

Frequency. The data concerning the frequency of intercapillary glomerulosclerosis from the Mallory Institute of Pathology are given in Table II and include figures from each year from 1934 through 1946 as well as the grand total for this thirteen-year period. Intercapillary glomerulosclerosis was found from four to fifteen times each year and 100 times in 9,824 autopsies. The yearly percentage of diabetics demonstrating intercapillary glomerulosclerosis at postmortem examination varied from 15 to 39 per cent and averaged twenty-six per cent for the thirteen-year period. The consistency of these findings from year to year and the large size of this series indicate that the results are significant. In other words intercapillary glomerulosclerosis is found in about 1 per cent of routine autopsies and in about 26 per cent of autopsies on diabetics. These percentages stress the importance of the subject.

TABLE I
AGE

Age	Diabetics without Intercapillary Glomerulosclerosis		Diabetics with Intercapillary Glomerulosclerosis	
Group	No.	Per cent	No.	Per cent
0–9	1	.6	0	
10–19	1	.6		
20–29	4	2.3	0	
30–39	10	5.6	0	
40–49	23	13.1	7	7
50–59	38	21.5	26	26
60–69	47	26.7	33	33
70–79	44	25	28	28
80–89	8	4.5	6	6
Total	176		100	100
Average age	59.9		64.1	

Duration of Diabetes. Intercapillary glomerulosclerosis has been shown by previous workers usually to be associated with diabetes of long-standing and it is generally considered that with increasing diabetic years the incidence of intercapillary glomerulosclerosis rises. Figure 2 demonstrates the increasing incidence of intercapillary glomerulosclerosis with increasing duration of diabetes. When only 14 per cent of patients with diabetes of less than four years' duration show intercapillary glomerulosclerosis, the incidence rises to 64 per cent in diabetics of from ten to fourteen years' duration. The apparent fall of incidence of intercapillary glomerulosclerosis in diabetes of fifteen to twenty years' duration may be explained on the basis of increasing mortality in this group.

TABLE II
FREQUENCY OF INTERCAPILLARY GLOMERULOSCLEROSIS AT POSTMORTEM EXAMINATION OF ROUTINE AS WELL AS DIABETIC CASES

Year	No. of Autopsies	Number with Intercapillary Glomerulosclerosis	% Autopsies with Intercapillary Glomerulosclerosis	Autopsies on Diabetics	Diabetics without Intercapillary Glomerulosclerosis	% Diabetics with Intercapillary Glomerulosclerosis
1934	730	8	1.09	28	20	28
1935	704	4	.57	24	20	17
1936	714	12	1.68	43	31	28
1937	784	4	.51	18	14	22
1938	708	9	1.27	23	14	39
1939	856	6	.70	32	26	19
1940	1063	11	.84	47	36	33
1941	869	6	.69	40	34	15
1942	766	15	1.96	44	29	34
1943	686	7	1.02	19	12	37
1944	591	7	1.18	19	12	37
1945	618	6	.95	26	20	23
1946	735	5	.68	24	19	21
Total	9824	100	1.02	387	287	26%

Severity of Diabetes. It is admittedly difficult and inaccurate to attempt to classify diabetes on the basis of insulin requirement alone. However, in the absence of more reliable methods diabetes was considered to be mild when the insulin requirement was from 0 to 20 units, moderate from 20 to 40 units and severe when the requirement was 40 units or more. Applying these criteria to the diabetics with and without intercapillary glomerulosclerosis no significant difference was demonstrated in the distribution of degree of severity of diabetes between the two groups. (Fig. 3.) The majority of diabetics both with and without intercapillary glomerulosclerosis were using less than 20 units of insulin daily. One observation that is of considerable interest is an apparent significant discrepancy between the blood sugar levels and glycosuria. Forty-five or nearly half of the patients with intercapillary glomerulosclerosis showed mini-

mal amounts of glycosuria, yet at the same time the blood sugar in these forty-five patients ranged from normal to over 500 mg. per 100 cc. In twenty-eight instances the blood sugar was 200 mg. or over at the time glycosuria was minimal. It is not uncommon in elderly dia-

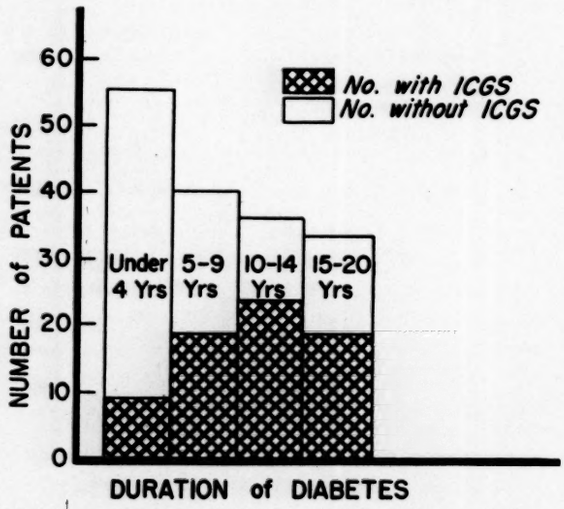

FIG. 2. Relationship of intercapillary glomerulosis to duration of diabetes.

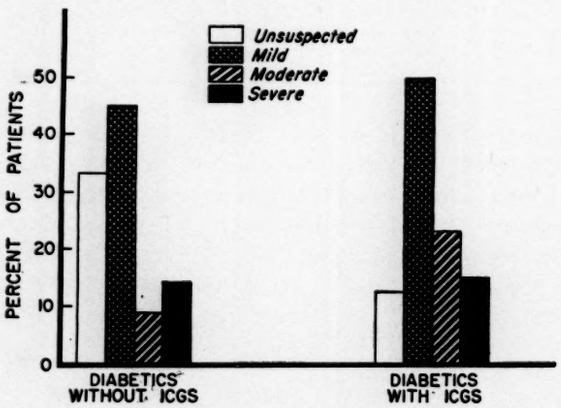

FIG. 3. Severity of diabetes.

betics to find a high blood sugar without as much glycosuria as might be observed in a younger patient with diabetes.[3] The mechanism in diabetics without renal disease has been shown to be an increased tubular resorptive capacity.[4] In diabetics with renal disease the glomerular filtration rate is lowered and this has been shown to hold in intercapillary glomerulosclerosis by Corcoran, Taylor and Page.[5] There is insufficient information in the cases in this series to determine whether or not elevated blood sugar with minimal glycosuria is of significance in aiding the clinical diagnosis of intercapillary glomerulosclerosis.

Hypertension. Figure 4 demonstrates a significant increase in the incidence of hypertension in diabetics with intercapillary glomerulosclerosis. Hypertension was divided into three grades of severity as follows: minimal when the systolic pressure ranged from 140 to 170 mm.

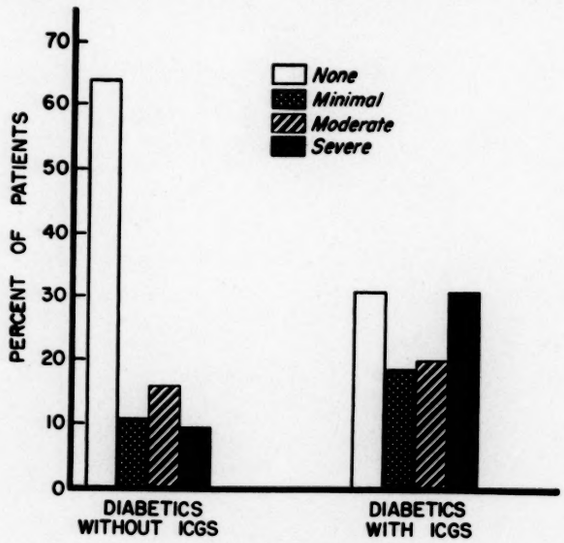

FIG. 4. Hypertension.

and the diastolic was 90 mm.; moderate when the systolic pressure ranged from 140 to 190 mm. and the diastolic 90 to 115 mm.; and marked when the systolic pressure was 190 or higher and the diastolic 115 or higher. Sixty-four per cent of the diabetic patients without intercapillary glomerulosclerosis were normotensive whereas only 31 per cent of those with intercapillary glomerulosclerosis had normal pressures. Conversely, the incidence of hypertension in intercapillary glomerulosclerosis was 69 per cent, nearly twice the 36 per cent incidence of hypertension in those with diabetes alone. This incidence of hypertension compares with that noted by other authors, yet in our experience the presence of hypertension in a diabetic was of little aid in arriving at a correct clinical diagnosis.

Albuminuria. Eighteen per cent of our diabetics without intercapillary glomerulosclerosis showed 3 or 4 plus albuminuria in contrast to 55 per cent of diabetics with intercapillary glomerulosclerosis. (Fig. 5.) Albuminuria was absent in only 3 per cent of those with intercapillary glomerulosclerosis whereas nearly 25 per cent of the diabetics showed no albumin in the urine. The difference in the figures is such to suggest that albuminuria is a significant

manifestation of intercapillary glomerulosclerosis and this has been the clinical experience of most observers.

Azotemia. There is a trend for azotemia to be greater in diabetics with intercapillary glomerulosclerosis, yet this difference is not striking. Other authors have reported similar observations.[6,7] (Fig. 6.) The non-protein nitrogen levels of the blood were below 40 in 41 per cent of the diabetic patients and in 26 per cent of those with intercapillary glomerulosclerosis. Eight per cent of the diabetics had non-protein nitrogen levels over 100 and 22 per cent of those with intercapillary glomerulosclerosis were in this range.

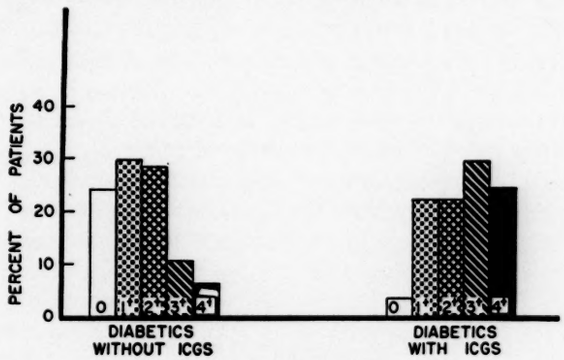

FIG. 5. Albuminuria.

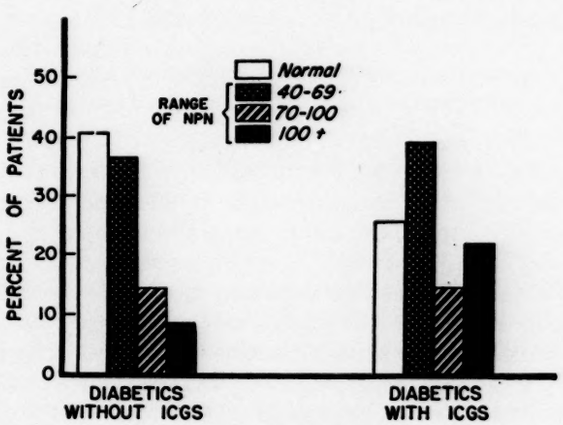

FIG. 6. Azotemia.

Edema and Cardiac Failure. Edema, dependent or generalized, was noted in 60 per cent of the diabetics with intercapillary glomerulosclerosis and in 24 per cent of those without intercapillary glomerulosclerosis. (Fig. 7.) In the majority of instances the edema was of dependent type and probably related to cardiac failure rather than to renal failure. This is borne out by Figure 8 which shows the difference in the incidence of cardiac failure which was present in nearly 60 per cent of the diabetics with intercapillary glomerulosclerosis whereas only 36 per cent of those without intercapillary glomerulosclerosis were in congestive failure. Henderson,[6] Rifkin et al.[8] and Lefeber and Dechard[9] have also noted that in the majority of instances the edema appeared to be related to cardiac failure.

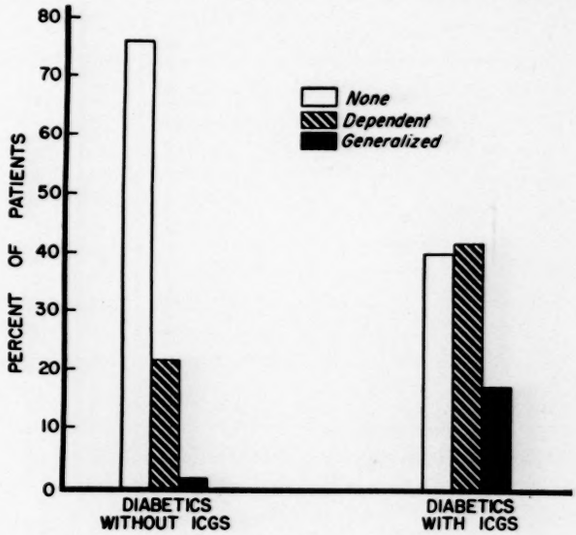

FIG. 7. Edema.

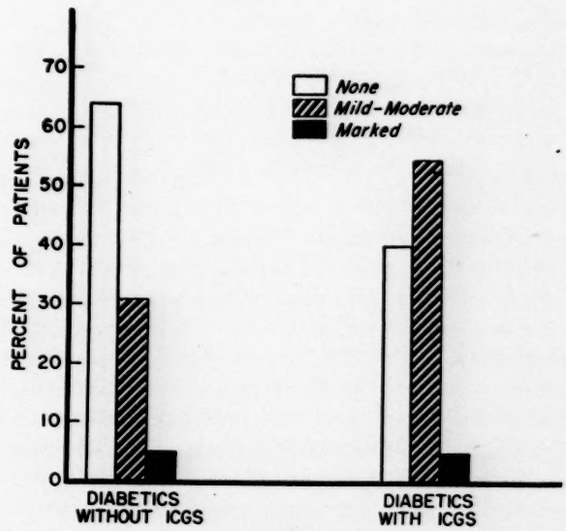

FIG. 8. Cardiac failure.

CAUSES OF DEATH

It is of interest to compare the causes of death, from the anatomic viewpoint, of the 100 patients with intercapillary glomerulosclerosis with a previously reported group of random diabetics.[10] Although the numbers of cases cited permit of

no great statistical significances, certain differences merit attention. (Table III.)

Cardiac decompensation appears somewhat more frequently in the intercapillary glomerulosclerotic group of patients, being present in 19 per cent as compared with the control group

TABLE III
CAUSES OF DEATH

	Diabetics without Intercapillary Glomerulosclerosis		Diabetics with Intercapillary Glomerulosclerosis	
	No.	Per cent	No.	Per cent
Coma	22	7.2	4	7
Cardiac decompensation	35	11.4	19	19
Myocardial infarction	31	10.0	12	12
Cerebral accident	15	4.9	12	12
Pulmonary infections including tuberculosis	73	23.8	12	12
Infections other than pulmonary	42	13.7	16	16
Renal decompensation with uremia	25	8.2	15	15
Other causes including unknown	44	21.0	10	10

incidence of 11.4 per cent. This difference is almost entirely due to an increased frequency of hypertensive heart disease in patients with intercapillary glomerulosclerosis, a finding that agrees well with the clinical significance of hypertension in this group. Although myocardial infarction appeared to be equally prevalent in the control and intercapillary glomerulosclerotic group, cerebral accidents were distinctly more common in the patients with intercapillary glomerulosclerosis. This finding may perhaps reflect the result of both the vascular degenerative disease common to both the heart and brain with the additional factor of intracerebral hemorrhage secondary to hypertension causing the increased frequency of cerebral accident in the experimental group of cases. Uremia as a cause of death is considerably more common in patients with intercapillary glomerulosclerosis (15 per cent) than in the diabetic population at large (8.2 per cent). Although seemingly at variance with the clinical evaluation that azotemia is not significantly more prominent in a group of patients with intercapillary glomerulosclerosis, this observation may only indicate that although it is not more common once present it is of grave significance, leading usually to progressive renal failure and death. This sequence of events is not at all unfamiliar to the clinician dealing with advanced diabetes. The incidence of uremia in this series of 15 per cent is somewhat lower than that reported by Rifkin et al.[8] (nine of twenty-two patients). This difference is very likely due to the fact that their cases were all instances of clinically recognizable intercapillary glomerulosclerosis and were in all probability patients with well advanced disease. The variations in the incidence of infections permit of no ready explanation save that since the patient with intercapillary glomerulosclerosis suffers as the result of the increased hazards of hypertension and renal involvement he dies less frequently of other causes, notably pulmonary infections.

CLINICAL COMPARISON OF FOUR GRADES OF INTERCAPILLARY GLOMERULOSCLEROSIS

The cases with intercapillary glomerulosclerosis were further classified according to the severity of pathologic renal changes in groups I to IV, the latter being the most severely involved. The four categories of severity of involvement of intercapillary glomerulosclerosis could then be compared with each other with respect to the clinical features previously cited. The size of the groups was too small to permit comparisons of statistical significance but certain trends became apparent and seem worthy of comment. When the four classes of intercapillary glomerulosclerosis were compared as to the duration of diabetes, no significant differences between the groups were noted. The trend, however, was for those with grade IV lesions to have been diabetic for longer periods of time than those with grade I intercapillary glomerulosclerosis. This trend can best be illustrated by observing the severity of the anatomic lesion in patients having diabetes for less than fifteen years and in those with diabetes of over fifteen years' duration. In the former group most patients had 1 to 2 plus intercapillary glomerulosclerosis with only eight of forty-nine patients showing the severe 4 plus lesion. In the latter group, that is the long term diabetics with a known history of over fifteen years' duration, most patients had 3 to 4 plus lesions, ten of eighteen having the most severe form of involve-

ment. This distribution leaves little doubt but that there is a definite relationship between duration of diabetes and severity of intercapillary glomerulosclerosis.

Severe hypertension was present in significantly greater incidence in grade IV cases than grade I. Fifty-five per cent of those with grade IV intercapillary glomerulosclerosis had severe hypertension in contrast to 9 per cent of those with grade I lesions. The severity of albuminuria correlated clearly with the degree of intercapillary glomerulosclerosis. Twenty-four per cent of those with grade I had 3 or 4 plus albuminuria whereas 76 per cent of those with grade IV intercapillary glomerulosclerosis had this amount of albumin in the urine. There was a tendency for azotemia to be more severe as the lesion of intercapillary glomerulosclerosis increased. It was also noted that in those with grade I lesions edema was less frequent than in those with grade IV lesions, the increase in incidence being from 44 to 84 per cent. Although cardiac failure was a prominent feature of intercapillary glomerulosclerosis when taken as a group, there was no clear correlation between the frequency of cardiac failure and the severity of intercapillary glomerulosclerosis.

COMMENTS

The results of a comparison of the clinical features of a group of diabetics with intercapillary glomerulosclerosis and a control group of diabetics without intercapillary glomerulosclerosis indicate differences suggesting that in the presence of this glomerular lesion certain clinical features are found in increased frequency.

Intercapillary glomerulosclerosis is more apt to occur in women but this is a reflection of the known increased incidence of diabetes in women over middle age. About one of every four diabetics will show intercapillary glomerulosclerosis at autopsy. It is of interest that in the years under study, 1934 to 1946, no increase in frequency was noted. Since intercapillary glomerulosclerosis is correlated with the duration of diabetes, an increased incidence may be anticipated in the future. The average age of a group of diabetics with intercapillary glomerulosclerosis is slightly greater than a similar group without intercapillary glomerulosclerosis. In the series reported the lesion was rare in patients under fifty years of age and was most common in those between the ages of fifty and seventy-nine, and is correlated with the duration of diabetes, being significantly increased in incidence in those patients with diabetes of over ten years' duration.

The frequency of occurrence of intercapillary glomerulosclerosis does not seem to be correlated with the severity of the diabetes. Although it is true that most patients with intercapillary glomerulosclerosis have mild diabetes, in all probability this is due to the fact that mild diabetes, as defined by insulin requirement, is more common than moderate or severe diabetes. In this series a discrepancy between the degree of elevation of blood sugar and the amount found in the urine was noted. Nearly half of the patients with intercapillary glomerulosclerosis had minimal amounts of sugar in the urine when their blood sugars were at such levels that one would expect large amounts of glucose to be present in the urine. Whether this phenomenon is more frequent in diabetics with intercapillary glomerulosclerosis than in those without was not determined. This observation may, however, have some importance in shedding light on cases of intercapillary glomerulosclerosis found in non-diabetic patients since it is possible that the diabetes may have been missed by virtue of the absence of urinary sugar and consequent failure to do blood sugar determinations. In three instances recently observed by one of the authors (S. L. R.) intercapillary glomerulosclerosis was found at postmortem examination in the absence of known diabetes. On investigating the histories and previous hospital records evidence of diabetes in the past was brought to light. It is therefore not unreasonable to postulate that in some of the reported instances of intercapillary glomerulosclerosis found in the absence of diabetes the clinical diagnosis of diabetes may have been overlooked due to transient or minimal glycosuria.

In diabetics with intercapillary glomerulosclerosis the incidence of hypertension was significantly increased. However, the most striking and most reliable criterion in the clinical estimation of intercapillary glomerulosclerosis appears to be the demonstration of 3 or 4 plus albuminuria. In general, when 3 to 4 plus albuminuria is found in a diabetic, intercapillary glomerulosclerosis is apt to be present. With less than this amount of albuminuria the diagnosis becomes increasingly doubtful. Electrophoretic analysis of plasma and urinary proteins may prove to be of diagnostic aid.[11]

The degree of azotemia in intercapillary

glomerulosclerosis was slightly greater. Edema and cardiac failure were likewise more frequent in this group and the edema was most frequently that which one would associate with cardiac failure.

The result of a comparison between a group

TABLE IV

Grade of Intercapillary Glomerulosclerosis	No. of Cases	No. with Classic Triad of Symptoms	Per cent
1	26	2	8
2	19	2	10
3	27	7	25
4	28	14	50

of diabetics with intercapillary glomerulosclerosis and a group without intercapillary glomerulosclerosis indicates that in diabetics with the renal lesion an increased incidence of severe hypertension, albuminuria, edema and cardiac failure can be demonstrated. The increased incidence of these clinical characteristics is of such a degree as to suggest that the etiologic factor related to these clinical stigmas is intercapillary glomerulosclerosis. However, hypertension, edema, cardiac failure and albuminuria occur with sufficient frequency in diabetes to make these findings of limited diagnostic value in distinguishing intercapillary glomerulosclerosis.

Of more importance than the incidence of the different individual clinical features is the frequency with which the edema, hypertension and albuminuria occur together in any one patient producing the so-called symptom complex. Considering this classic symptom complex as comprising 3 to 4 plus albuminuria and some degree of hypertension and edema, analysis of the patients with typical glomerular lesions revealed the presence of this diagnostic triad in twenty-five of one hundred cases (significantly the control diabetics presented five instances of the "classic syndrome").

A breakdown of these one hundred cases into the four grades of severity of the glomerular lesion demonstrated the presence of the so-called classic symptom complex in 8 per cent of the grade I cases, 10 per cent of the grade II cases, 25 per cent of the grade III and 50 per cent of the grade IV cases. (Table IV.) Although these correlations are of considerable interest, the reverse relationship may be more important, namely, that the classic clinical features were not present in approximately 75 per cent of the proved cases of intercapillary glomerulosclerosis and were absent in over 50 per cent of the patients with more severe lesions. It is of equal significance that five of the control diabetics presented the "classic syndrome." It is apparent that in any given instance the presence of the classic features does not necessarily indicate with certainty the presence of the glomerular lesion. It is equally clear that the anatomic lesion is often not associated with the diagnostic clinical triad of findings.

SUMMARY AND CONCLUSIONS

One hundred diabetics with proven intercapillary glomerulosclerosis were compared clinically with 176 diabetics not having this glomerular lesion. It was thus hoped that certain clinical differences might be revealed that would be of help in establishing the diagnosis of intercapillary glomerulosclerosis in any individual patient. The following points of interest were found:

With increasing duration of the diabetes there was a definite increase in the incidence of intercapillary glomerulosclerosis. Whereas only 14 per cent of the patients with diabetes of less than four years' duration had this renal lesion, the incidence rose to 64 per cent in patients with diabetes of ten to fourteen years' duration. No significant difference was found in the severity of the diabetes between the group of patients with intercapillary glomerulosclerosis and the control group. In passing it was noted that the patients with this specific glomerular lesion tended to show less glycosuria than was expected from the associated levels of hyperglycemia. The significance of this observation is discussed. Hypertension, albuminuria, azotemia and cardiac failure all were more frequent and more severe in the patients with intercapillary glomerulosclerosis. The causes of death of this group of 100 patients were likewise compared with those of a control group of diabetics. It became evident that uremia, cardiac decompensation and cerebrovascular accidents were significantly more prevalent among these patients than in the control group.

When the patients with intercapillary glomerulosclerosis were divided into four categories on the basis of the severity of involvement of the kidneys, certain differences were observed.

Patients with the most extensive grade IV lesion tended to have more severe edema, hypertension, albuminuria and cardiac failure than the less severely involved grade I group. Moreover, the grade IV patients were, on the whole, diabetics of longer duration than the other patients.

Perhaps of greatest importance is the problem of how often these various features occur together in any individual patient to produce a clinically recognizable syndrome. This occurred in twenty-five of the one hundred patients with intercapillary glomerulosclerosis. It also occurred in five of the control group of diabetics. The conclusion was clear: Many if not most cases of intercapillary glomerulosclerosis do not present the classic triad of clinical findings; moreover, the classic pattern may occasionally be found in diabetic patients not having intercapillary glomerulosclerosis. As was said before, the entity is more often missed clinically than misdiagnosed.

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Intercapillary Glomerulosclerosis: A Clinical and Pathologic Study

*III. A Pathologic Study of 100 Cases**

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The specificity of the pathologic lesion in the Kimmelstiel-Wilson syndrome has remained fully as controversial as the identity of the clinical entity. The reports in the literature agree very poorly as to the relationship of this syndrome to diabetes mellitus and disagree over the diagnostic specificity of the glomerular histologic lesion.[1–7]

Much of this confusion may be due to the ambiguity of the term intercapillary glomerulosclerosis. On the one hand it is used to denote a specific entity, the Kimmelstiel-Wilson syndrome, and on the other hand it may be used in a completely non-specific sense as a purely descriptive histologic term. In their first description Kimmelstiel and Wilson on purely anatomic grounds selected eight cases of glomerular lesions which, by virtue of their distinctive characteristics, segregated themselves into a unique homogenous pathologic group.[8] To these cases they applied the term "intercapillary glomerulosclerosis." However, in this original report they failed to emphasize the fact that this group of cases represented only one distinctive form of intercapillary glomerulosclerosis among a great variety of other types of non-specific intercapillary glomerulosclerosis. It is well known that in many forms of renal disease such as nephrosclerosis, glomerulonephritis and others glomerular damage may be sustained that will evidence itself in glomerulosclerosis, fibrosis and axial thickening. Since these sclerotic changes affect the mesangium of the glomerulus and the basement membrane of the capillary tufts in the glomerulus, they occupy or appear to occupy an intercapillary situation. All of these changes then, in a descriptive sense may be called intercapillary glomerulosclerosis. However, it should be clearly appreciated that they do not reproduce the specific type of nodular glomerulosclerosis originally described by Kimmelstiel and Wilson which for purposes of clarity, as Bell[9] and Kimmelstiel and Porter[10] have stated, would be better termed nodular intercapillary glomerulosclerosis or the Kimmelstiel-Wilson lesion. If, then, this specific type of glomerular lesion is sharply separated from the general group of non-specific changes, it has been found in our experience to be limited to diabetes alone as a pathognomonic feature when present.[11] As previously cited in Part II of this presentation in the course of the routine diagnostic postmortem pathology performed at this laboratory occasional instances of this specific lesion have been encountered in patients apparently non-diabetic.[11] In each such case a painstaking search into the past history has uncovered the existence of diabetes mellitus at some earlier date. It is probable in these cases that with the passage of time the diabetes had ameliorated to the point where routine urinalysis in the final entry failed to demonstrate any glycosuria. The anatomic glomerular lesion, however, persisted as a permanent residual of the pre-existing diabetes mellitus.

It is the purpose of this section of the presentation to attempt to describe this specific type of intercapillary glomerulosclerosis, separating it from the wide variety of non-specific degenerative changes that may affect the glomerulus, as well as from the inflammatory lesions that may simulate nodular intercapillary glomerulosclerosis.

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FIG. 1. Normal glomerulus showing fine linear basement membrane. (Lee-Brown modification of aniline blue stain, × 750.)

FIG. 2. Glomerular tuft showing considerable axial thickening arising in the hilus and extending fanwise out to the periphery. (Lee-Brown modification of aniline blue stain, × 750.)

MATERIAL

These studies are based upon cases selected from the files of the Mallory Institute of Pathology of the Boston City Hospital. One hundred cases of diabetes having the classic glomerular lesion conforming to the original description of Kimmelstiel and Wilson as well as approximately 200 diabetics without glomerular lesions form the main body of the pathologic study. Additional non-diabetic cases of benign nephrosclerosis occurring in the older age group were likewise selected for comparison together with a small group of cases of chronic intracapillary glomerulonephritis.

PATHOLOGIC DESCRIPTION

The typical diagnostic lesion of intercapillary glomerulosclerosis is found within the glomerular capillary tuft. The capillaries of a normal glomerulus are suspended or arranged on a delicate connective tissue framework or axial stroma. These capillaries are covered by an enveloping epithelial membrane which is reflected from the glomerular tuft to become continuous with the lining cells of Bowman's capsule and which in turn is continuous with the neckpiece of the proximal convoluted tubule. Thus although it is not readily apparent in ordinary tissue stains, the peripheral loops of capillaries are actually comprised of two layers of cells separated by a basement membrane, an outer epithelial and an inner vascular endothelial. These finer histologic details are well brought out by basement membrane stains such as the Lee-Brown modification of the Mallory aniline blue stain. Moreover, these capillaries rest on an extravascular connective tissue support which is thus an intercapillary substance termed the mesangium.[12–14] (Fig. 1.)

The lesion of intercapillary glomerulosclerosis observed in diabetics is not only an accentuation of, but also a particular form of thickening of the axial stroma so frequently seen in nephrosclerotic kidneys. In the nephrosclerotic kidney the axial thickening starts at the hilus of the glomerular tuft and is often continuous with the hyaline thickening of the afferent arteriole and extends rather uniformly with decreasing intensity toward the periphery of the tuft.[15] (Fig. 2.) Discrete peripheral nodular hyaline masses are never produced. It is, however, these cases of marked nephrosclerosis, not necessarily occurring in diabetics, that have evoked so much of the controversy. They have been justifiably described as intercapillary glomerulosclerosis and have then been incorrectly cast into the Kimmelstiel-Wilson syndrome along with the specific lesions to be described.

In fairly sharp contrast, the lesion of intercapillary glomerulosclerosis is most marked at the periphery of the glomerulus with relatively little involvement of the hilar region. The earliest lesion is composed of a slight hyaline deposition within the periphery of the glomerulus, embedding occasionally contiguous epithelial cells as well as the stromal fibroblastic cells, remaining well outside of the capillary basement membrane. Soon a small hyaline mass is seen surrounded by a zone of nuclei. (Fig. 3.) The many nuclei are due to a crowding or pushing of previously normal cells toward the periphery of the hyaline mass. Characteristically, a peripheral capillary remains forming a halo about the contiguous portion of the

3 4 5

FIG. 3. A solitary hyaline nodule of intercapillary glomerulosclerosis. In the periphery of the nodule are seen nuclei of either fibroblastic or epithelial origin. (Phloxine-methylene blue stain, × 300.)

FIG. 4. A lesion of intercapillary glomerulosclerosis showing the "halo" effect of a peripheral intact capillary channel; note the accompanying thickening of the associated arteriole and the diffuse axial thickening of the glomerular tuft. (Lee-Brown modification of the aniline blue stain, × 300.)

FIG. 5. A markedly involved glomerulus with many discrete hyaline nodules, each with a preserved intact peripheral capillary. (Lee-Brown modification of the aniline blue stain, × 300.)

6 7 8

FIG. 6. A low power view showing marked involvement of the kidney with all but one glomerulus containing multiple hyaline masses. (Phloxine-methylene blue stain, × 75.)

FIG. 7. A markedly involved glomerulus showing both nephrosclerotic diffuse axial thickening and peripheral discrete nodular thickenings associated with capsular adhesions and periglomerular fibrosis. (Phloxine-methylene blue stain, × 300.)

FIG. 8. Glomeruli demonstrating far advanced intercapillary lesions with complete obliteration of the capsular space in one. (Phloxine-methylene blue stain, × 200.)

hyaline mass. This capillary is patent, at times engorged, and may even be aneurysmal. (Figs. 4 and 5.) The basement membrane of the capillary not in contact with the hyaline mass remains intact, as is best demonstrated with the Lee-Brown stain. In the classic lesion the endothelial and epithelial cells of the glomerulus show no tendency toward swelling or proliferation as seen in glomerulonephritis.

The degree of involvement of a single glomerulus varies, as does the number of glomeruli so involved. Many glomeruli contain only one hyaline mass while others contain from two to six masses in the axial stroma. (Fig. 5.) In general, when many hyaline masses are present in any single glomerulus, the majority of the glomeruli throughout the kidney are involved by the process. (Fig. 6.) Such cases, classified in the previous sections of this study as 4 plus, we have considered as markedly involved and have found to present the clinical syndrome most often. In far advanced lesions as the nodular masses increase in size, capsular adhesions may develop with periglomerular fibrosis and eventual complete obliteration of the capsular space and total fibrosis of the glomerular tuft. (Figs. 7 and 8.) Even in complete hyalinization of the glomerulus with the phloxine-methylene blue stain discernible opaque eosinophilic masses of the pre-existing intercapillary glomerulosclerosis remain in contrast to the lighter pink hyalinization of the remainder of the glomerulus. In most kidneys with maximal intercapillary glomerulosclerosis the hyaline mass is as characteristic in its appearance as in the minimally involved kidney.

Bowman's capsule may be involved in the process, as previously suggested. The degree

of involvement varies considerably. Frequently a deposition of homogeneous pink material is seen between the epithelial lining and the basement membrane. This material later becomes hyalinized. As the capsular hyalinization becomes more extensive, there is a conspicuous laminated appearance which is due to concentric layers of connective tissue. Bowman's space therefore becomes narrowed by the capsular change and eventually may become obliterated. (Fig. 8.) These capsular changes are not specific to intercapillary glomerulosclerosis and are seen in many forms of nephropathy. Since there is usually in these marked cases some arteriolosclerotic involvement occurring concomitantly with the intercapillary glomerulosclerosis, it cannot be assumed that these capsular glomerular changes are specific for the intercapillary glomerulosclerosis.

As in all forms of renal disease it is these far advanced cases of nodular intercapillary glomerulosclerosis that produce the great difficulty in interpretation. In these instances marked destruction of the glomeruli may occur with obliteration of the capsular spaces and total fibrosis of the entire glomerulus, burying the nodular masses within an over-all collagenous connective tissue. It can readily be imagined that such far advanced lesions may closely resemble the destructive fibrosis of glomeruli that occurs as the end result of any form of renal disease, especially glomerulonephritis.

In glomerulonephritis either the capsular epithelium may be primarily involved, so-called extracapillary glomerulonephritis, or the vascular endothelium may be primarily affected, termed intracapillary glomerulonephritis. In either instance if the process becomes chronic, particularly the latter, the intercapillary connective tissue, the mesangium and the basement membranes of the capillary will inevitably be affected. In the later stages of these inflammatory processes fibrosis and thickening of the mesangium may produce lesions closely resembling intercapillary glomerulosclerosis. However, the basic inflammatory nature of the disease with its characteristic cellular proliferation, crescents, large avascular glomeruli, collapsed capillaries and glomerular adhesions should all serve to separate the concomitant intercapillary fibrosis from the purely degenerative form of Kimmelstiel-Wilson lesion. Perhaps only in the most far advanced examples of glomerulonephritis and intercapillary glomerulosclerosis, when all that remain are masses of collagen replacing the glomeruli, should the two entities become indistinguishable.

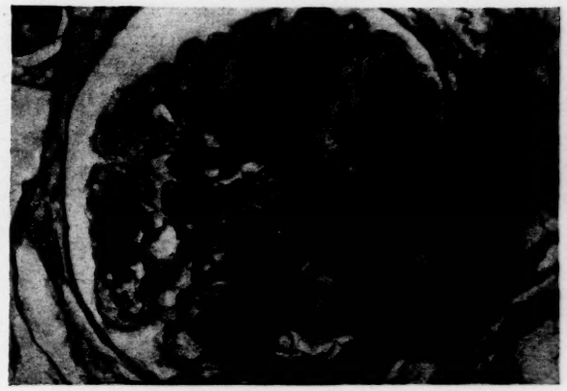

FIG. 9. The coexistence in one glomerulus of diffuse nephrosclerotic axial thickening and nodular intercapillary glomerulosclerosis, the one by no means obscuring the other. (Lee-Brown modification of the aniline blue stain, × 750.)

Afferent arteriolar changes are usually found in intercapillary glomerulosclerosis. (Fig. 9.) Marked narrowing of the lumen of these arterioles by hyalinedegeneration of their muscular walls is the common change. The coexistence of these severe arteriolar lesions with the nodular glomerular lesions in diabetes adds considerably to the difficulty of differential diagnosis. In the majority the narrowing can be followed in serial sections to extend continuously with the axial fibrosis of the glomeruli. (Fig. 9.) The narrowing may be quite extreme at the hilus of the glomerular tuft. In other glomeruli the afferent arteriole may appear entirely normal throughout the greater part of its course, but occasionally at one or more sites a large hyaline mass or plaque projects into the lumen, almost completely occluding the arteriole. In the great majority, if not all of the glomeruli involved by intercapillary glomerulosclerosis, the afferent arteriole supplying the respective glomerulus contains hyaline changes of considerable importance either diffusely or in foci throughout their course. Arteriolar changes are found most often in kidneys showing marked to moderate intercapillary glomerulosclerosis. An occasional case with minimal intercapillary glomerulosclerosis may have apparently normal afferent arterioles. These rare cases of intercapillary glomerulosclerosis unassociated with arteriolar lesions are of great significance since they offer considerable support to the hypothesis that intercapillary glomerulosclerosis is not simply an extension of the non-specific de-

generation but rather is a specific glomerular degenerative change occurring in diabetes.[16]

The lumens of the efferent arterioles may also be narrowed by hyalinization, usually less extensively. In the early lesions there is apparently little narrowing. Invariably in the more extensively involved kidney the efferent arteriole shows some degenerative hyaline changes. We have been unable to confirm the impression of other writers that the absence of efferent arteriolar involvement is a characteristic of diabetics.

TABLE I
ASSOCIATED RENAL DISEASES

Severity of Involvement of Intercapillary Glomerulosclerosis	1+	2+	3+	4+
No. of cases	25	19	27	29
Average combined weight of kidneys (gm.)	330	382	338	341
Acute and/or chronic pyelonephritis	2	1	2	3
Glomerulonephritis	0	0	0	3
Malignant nephrosclerosis	0	0	0	2
Benign nephrosclerosis (severe to moderate)	10	11	11	13

There appears to be no direct correlation between the involvement of the main renal arteries and its larger branches and intercapillary glomerulosclerosis.

Tubular lesions such as fatty degeneration and glycogen deposition are found not uncommonly in these diabetic kidneys.[16] Since they are no more common or severe in diabetic patients with intercapillary glomerulosclerosis than they are in diabetics without intercapillary glomerulosclerosis, they cannot be construed to have any differential diagnostic value.

To the best of our knowledge there is no gross appearance of the kidneys characteristic of intercapillary glomerulosclerosis. The majority of cases show the granular cortical surface of benign nephrosclerosis with narrowing of the cortex and gaping, thick-walled arteries on the cut surface. The color is slightly pale, yellow-brown, but not at all characteristically altered.

Many of the cases included in the present series showed other renal diseases in addition to the intercapillary glomerulosclerosis. These associated diseases may have at times masked or certainly altered the clinical picture. Table 1 shows the various associated renal lesions. No attempt has been made to include minor lesions such as glycogen nephrosis, focal healed pyelonephritis, infarcts or insignificant small tumors.

COMMENTS

From the preceding study certain considerations merit discussion. In the files of the Mallory Institute of Pathology of the Boston City Hospital over the past twelve years no cases of intercapillary glomerulosclerosis of the nodular variety have been encountered in non-diabetic patients. This fact does not stem from the exclusion of the anatomic diagnosis in the absence of diabetes since in the present study the clinical history was not known prior to establishment of the anatomic diagnosis. Moreover, the few apparent discrepancies in this constant association were resolved by recourse to the past histories of these patients, which revealed the presence of pre-existing diabetes. In passing, it is worthy of mention that this problem of amelioration of diabetes, as well as lack of glycosuria despite some considerable hyperglycemia in the patient with intercapillary glomerulosclerosis, seems of more than coincidental interest. A study of this interesting group of cases is intended.

With regard to the specificity of the histologic lesion, it has been demonstrated that other forms of chronic renal disease affect the glomerulus in a manner that closely simulates the nodular lesions of intercapillary glomerulosclerosis. Chief offender in this regard is severe benign nephrosclerosis which is not uncommonly found in diabetic patients. As has been demonstrated, although benign nephrosclerosis indeed produces a type of intercapillary glomerulosclerosis, these glomerular lesions should be readily separable from the specific nodular variety of Kimmelstiel-Wilson.

In the majority of cases the moderate to marked hyalinization of the afferent or efferent arteries that exists is not considered an intrinsic portion of the lesion but is rather considered to be concurrent nephrosclerosis. Many cases present certain capsular changes but such changes are not a constant finding and have no specificity.

Exclusion of the diffuse variety of intercapillary glomerulosclerosis found in benign nephrosclerosis from the Kimmelstiel-Wilson syndrome considerably clarifies the clinical picture, re-

moving as it does the non-diabetics from the Kimmelstiel-Wilson group of cases.

The only other form of nephropathy that may produce serious difficulty by simulating nodular intercapillary glomerulosclerosis is chronic glomerulonephritis of the intracapillary type. Although this entity may produce focal areas of glomerular fibrosis that in any given high power field may resemble the diabetic lesion, examination of several glomeruli or, better yet, the entire slide will soon disclose the essentially inflammatory proliferative nature of this process in contrast with the degenerative nature of the Kimmelstiel-Wilson lesion.

The histologic criteria which should be fulfilled before the diagnosis of intercapillary glomerulosclerosis is made are as follows: (1) the presence of one or more peripheral eosinophilic hyaline masses in the apparent axial stroma of the glomerular tuft; (2) the presence of a peripheral capillary forming a partial or complete halo about the hyaline mass; the peripheral capillary is best seen in kidneys congested with blood; in such cases the capillary containing red cells appears to have aneurysmal projections into Bowman's space; (3) no evidence of significant endothelial cell or epithelial cell proliferation of the glomerular tuft.

The exact site of origin of this nodular material, its chemical compositions and its specific staining reactions are all problems of intense interest at the present time. Allen, among others, has pointed out qualitative aspects of this hyaline material which help to differentiate it from types of hyalin found in other nephropathies.[4] He has pointed out its relative resistance to tryptic digestion as well as its curious lamination and fibrillar composition. The present study has not pursued these lines and cannot add to these problems. In addition, although we have adhered throughout this presentation to the use of the term intercapillary glomerulosclerosis, it is requisite at this time to point out that no agreement has yet been reached as to whether this apparently hyaline deposit actually arises in the mesangium or in the capillary basement membrane.

SUMMARY AND CONCLUSION

The present study indicates that the Kimmelstiel-Wilson lesion is a specific histologic lesion found only in diabetics. Although nephrosclerotic and glomerulonephritic changes may closely simulate it, specific histologic points of difference have been pointed out. Much of the current confusion in the literature has arisen out of the use of the term intercapillary glomerulosclerosis in a purely descriptive sense. This general use of the term has failed to take into cognizance the fact that Kimmelstiel and Wilson in their original description segregated from this diffuse variety of intercapillary lesions a specific peripheral nodular variety that remains to this date a distinct entity. Substitution of the more specific terms, Kimmelstiel-Wilson lesion or nodular intercapillary glomerulosclerosis, for the previous terminology would do much to clarify the confusion surrounding this clinical syndrome.

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Seminars on Congenital Heart Disease

Congenital Pulmonary Stenosis*

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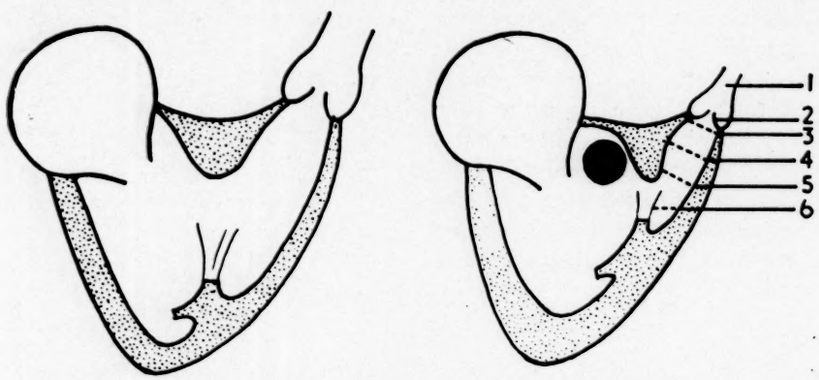
The term congenital pulmonary stenosis is often used loosely to denote one or more types of obstruction to the blood flow without any qualification at all. Clearly it means no more than a congenital narrowing of the tract along which blood flows to the lungs. The obstruction may be of various types and at various levels. (Fig. 1.) Thus it may be situated as follows: (1) in the pulmonary artery (pulmonary atresia); (2) at the pulmonary valve (valvular stenosis); (3) in the outflow portion of the right ventricle, the infundibulum (infundibular stenosis); (4) in the inflow portion of the right ventricle (tricuspid atresia).

It is a difficult task in a short article to give more than a brief survey of the anatomic types; moreover, one type may accompany another or may be a concomitant of a different anomaly. Thus a valvular or infundibular stenosis usually accompanies tricuspid atresia; valvular and infundibular stenosis may co-exist; either may be present with transposition of the great vessels. In this article the chief presentation will be of valvular stenosis and infundibular stenosis.

INCIDENCE

Pulmonary Valvular Stenosis with Closed Interventricular Septum. This is the type that has been called "pure" pulmonary valvular stenosis; the term is convenient but not entirely satisfactory because in a proportion the foramen ovale is patent. The term, "trilogy of Fallot," as used by the French, has little to commend it.



1A 1B

Fig. 1. Essential structure of the right ventricle and of pulmonary stenosis as seen in the Fallot group. A, inflow and outflow portion (infundibulum) of the ventricle; B, the infundibulum is seen to be small and associated with an interventricular septal defect (dark patch); the various levels at which the actual effective stenosis may occur are indicated: (1) pulmonary atresia; (2) valvular stenosis; (3) high, (4) intermediate and (5) low infundibular stenosis; (6) subdivision of right ventricle.

The condition has often been said to be very uncommon but during the last few years it has become increasingly recognised and it is now accepted to occur fairly frequently. It is important to recognise it in order to ensure that the correct treatment, namely pulmonary valvulotomy, is applied, and not an anastomosis. The exact incidence is difficult to assess but Maude Abbott (1936), in her 1,000 cases of congenital malformation of the heart, included 110 with pulmonary stenosis, excluding forty with pulmonary atresia; this compares with

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ninety-two cases of patent ductus arteriosus and seventy of aortic coarctation. The ventricular septum was patent in eighty-five of the 110 cases (they were of the Fallot type) and closed in twenty-five; in these twenty-five the foramen ovale was patent in sixteen and closed in nine.

During the last four years I have, myself, operated upon forty-three patients; from the steadily increasing literature and experiences of others it is clear that many more cases are now being recognised.

Pulmonary Valvular Stenosis with Patent Interventricular Septum. Just as pure pulmonary valvular stenosis was thought to be rare so it has been taught, and indeed often still is, that valvular stenosis is uncommon in the tetralogy of Fallot. If it is sought for carefully and properly, it is found to be quite common, the incidence being between 40 and 50 per cent of all cases. One reason for failure of recognition of the condition is the practice in the Blalock and Potts operations of merely opening the chest, performing the anastomosis and not making any attempt to inspect the stenotic lesion itself. My own policy is, after careful preoperative investigation, to expose the heart in all cases and, in addition to making an external inspection, to introduce a catheter through the wall of the right ventricle and by means of an electromanometer to take pressure tracings so as to identify the exact level of the obstruction. In my last fifty cases a valvular stenosis was present and was treated by valvulotomy in twenty-six; in seven of these it was combined with an infundibular stenosis; in nineteen it was solitary. The incidence was therefore 38 per cent or 52 per cent if combined with infundibular stenosis. Apart from these figures Keith (1909) found a valvular stenosis in 25/63 (40 per cent) of cases of Fallot's tetralogy; Brown (1939) states it is present in "about half," and Sellors and Belcher (1950) found it in twenty of sixty-five cases (30 per cent).

Infundibular Stenosis. Rarely this may exist as an isolated lesion without patency of the septa. I have seen and operated upon two such patients. Abbott (1936) knew of two and both Peacock (1866) and Keith (1909) mention the condition.

Typically it occurs as part of the tetralogy of Fallot and from my own experiences in my last fifty cases, quoted previously, an infundibular stenosis was present in twenty-four (48 per cent) and in a further seven was present in company with a valvular stenosis, giving thirty-one (62 per cent).

FIG. 2. Photograph of specimen of pure pulmonary valvular stenosis; note the tiny orifice and the dilated pulmonary artery.

MORBID ANATOMY

Pulmonary Valvular Stenosis with Closed Interventricular Septum. Several characteristic features may be observed in this condition. The valvular stenosis is caused by fusion of the cusps which form a diaphragm-like or conical obstruction with a small central stoma 2 to 4 mm. in diameter; the pulmonary artery always exhibits a marked post-stenotic dilatation. (Figs. 2, 4 and 5.) The general effect of the projection of the conical valve resembles that of the cervix uteri, although of course much smaller. In late cases the small orifice may carry warty vegetations or even be calcified; exceptionally the valve may be calcified.

The right ventricle is usually grossly hypertrophied, its walls being often as much as 2 cm. in thickness, pale and showing white patches of fibrous replacement. Frequently the subvalvular region shows the subendocardial "icing" characteristic of the congenital deformation seen in Fallot's tetralogy, and confirms that the fusion of the valve cusps (or perhaps their non-separation) is due to an error of development and is not acquired through "foetal endocarditis."

The foramen ovale may be widely open, a mere slit or may be closed.

In Fallot's Tetralogy. It is uncommon to see the gross generalised post-stenotic dilatation of the pulmonary artery which is more commonly much smaller than normal and its distal portion

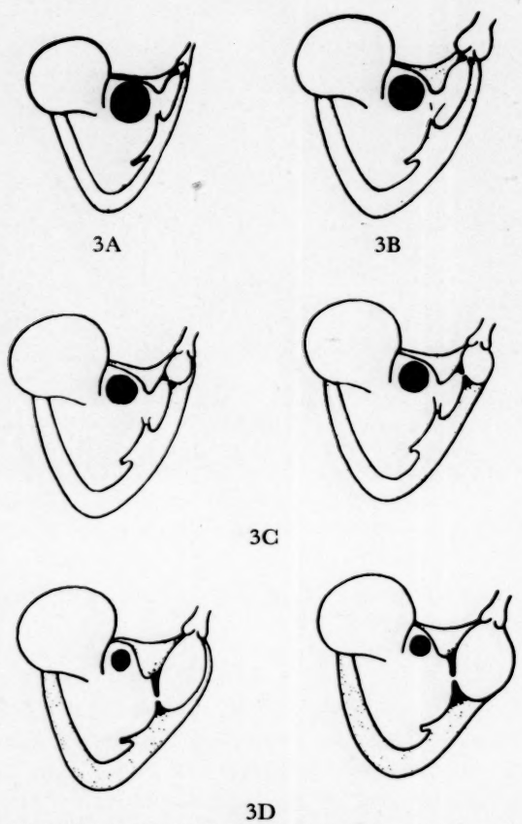


FIG. 3. Types of infundibular stenosis; A, hypoplasia; B, high; C, intermediate; D, low. A septal defect is shown in all.

is especially small and narrow. The proximal part is dilated but strictly in conformity with the globe-like projection formed by the projecting, fused valve. The fused valve cusps typically form a much more globular structure than in pure valvular stenosis, although a simple cone or even a flat dome may be present. Often the valve is bicuspid and its fused structure is plainly visible. Sometimes the fusion or development is uneven so that the valve is eccentric; this is particularly so in cases of valvular atresia.

Although the wall of the right ventricle is thickened (1 cm. or more in an adult) it never shows the extreme hypertrophy seen when the interventricular septum is closed; presumably it is spared in part by the patency.

Infundibular Stenosis. A great deal of loose writing and loose thought is encountered in regard to infundibular stenosis. It is commonly described, quite wrongly, as being of a long tubular nature, fibrous or muscular or both. This error has arisen partly through faulty observation and especially because specimens are inspected after death in a state of rigor mortis or, worse still, when hard and contracted through formalin fixation. If the heart is examined when not fixed and contracted, and particularly when it is alive and pulsating, as at operation, the state of affairs is seen to be quite different.

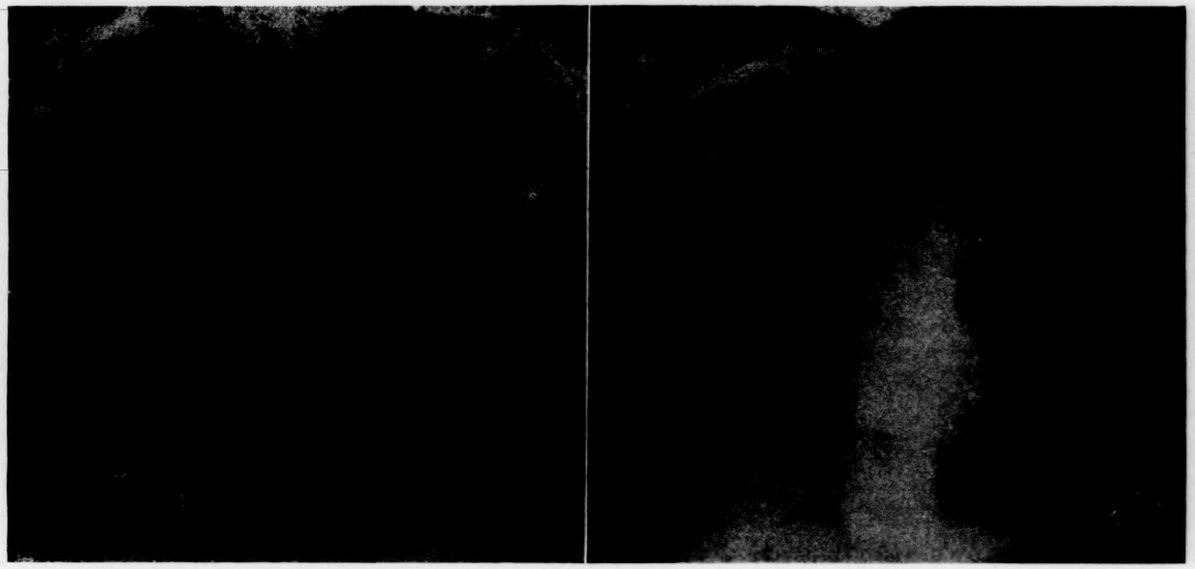
The basic structure of the right ventricle (Fig. 1A) consists of an inflow and an outflow portion; in the tetralogy of Fallot the outflow portion (infundibulum) is found to be hypoplastic to a greater or lesser degree (Fig. 1B), but as a rule its effective lumen is adequate; the actual stenosis occurs at one level within it and is linear or diaphragmatic. Even in these cases in which the infundibulum is so hypoplastic as to constitute a long obstruction there is always a secondary level of more complete stenosis. (Fig. 3A.)

The stenosis may be high (Figs. 1B and 3B), intermediate (Figs. 1B and 3C) or low. (Figs. 1B and 3D.) A valvular stenosis may co-exist.

Post-stenotic dilatation is always seen and is an important practical and diagnostic feature. When the stenosis is high, close to the valves, the post-stenotic dilatation affects the first part of the artery, distending and obliterating the sinuses of Valsalva. In the intermediate and low forms an infundibular chamber is formed between the stenosis and the pulmonary valve; the sinuses of Valsalva are usually recognisable. The outer wall of the chamber may be muscular in which case it does not project above the surface; but if, as is often the case, it is deficient in muscle, the chamber projects so as to be observed radiologically and readily noticeable at thoracotomy, a feature invaluable in diagnosis. The stenosis itself is based on a muscular shelf or projection but its edges are thin and fibrous, the whole appearance often being of a small aperture in a diaphragm-like structure; its edges may show warty vegetations.

CLINICAL MANIFESTATIONS

Valvular Stenosis with Closed Interventricular Septum. The clinical picture is varied and may be roughly considered in four types, chiefly



4A 4B

FIG. 4. A and B, plain radiograph and angiocardiogram to show post-stenotic dilatation of pulmonary artery.

decided by the severity and the patency or otherwise of the foramen ovale.

(1) There may be no symptoms at all; no cyanosis or disability, and the signs of valvular stenosis may be noticed as a result of routine examination. These cases may later progress to one of the other types.

(2) Some symptoms may be noticed early in life, such as diminished exercise tolerance, dyspnoea or even occasional mild cyanosis on exertion. Typically the onset of cyanosis is delayed, perhaps until adult life, and occurs when the presence of a patent foramen ovale allows a right-to-left interatrial shunt to develop as the pressure rises behind the pulmonary stenosis. Finger clubbing will develop later also.

(3) Cyanosis and disability are noticed from birth; finger clubbing is also present. It is in these cases that a misdiagnosis of Fallot's tetralogy is often made.

(4) The foramen ovale is closed and so central cyanosis and finger clubbing are not seen, although some peripheral cyanosis of the cheeks is common. The chief feature is dyspnoea on exertion and increasing disability, usually accompanied with pulsating neck veins and a large pulsating liver.

A notable feature in all types is the absence of squatting, so constant in Fallot's tetralogy.

On clinical examination the size of the heart is variable; it may be normal but characteristically it is enlarged with marked right ventricular uplift. A basal systolic thrill and a basal systolic murmur, maximal in the pulmonary area, are typical but the thrill may be absent or difficult to feel. The murmur may be soft and localised (especially in severe cases) or may be loud, harsh, of a "sawing wood" character and heard all over the precordium and conducted widely to the back of both chests. It is often impossible on auscultation alone to decide whether the stenosis is valvular or infundibular.

Radiologically the lung fields show diminished vascularity (except in mild cases), but the main right and left pulmonary arteries are often dilated. The most striking feature is the post-stenotic dilatation of the main pulmonary artery (Fig. 4) which may be so great as to be mistaken for an aneurysm and which contrasts with the small aorta. Occasionally, when the heart is very large, the dilated pulmonary artery may not be visible as it is pushed up to lie horizontally as a result of the great hypertrophy of the right ventricle which conceals it. (Fig. 5.) The enlargement of the heart is an important radiologic feature and contrasts with the normal size or only moderate enlargement seen in the Fallot type of case. The enlargement is seen on fluoroscopy to be due chiefly to the right ventricle and the right atrium. The electrocardiogram shows right ventricular preponderance and an important feature shown in the chest leads is inversion of the T waves, perhaps with S-T depression, across as far as V_5 or even V_6.

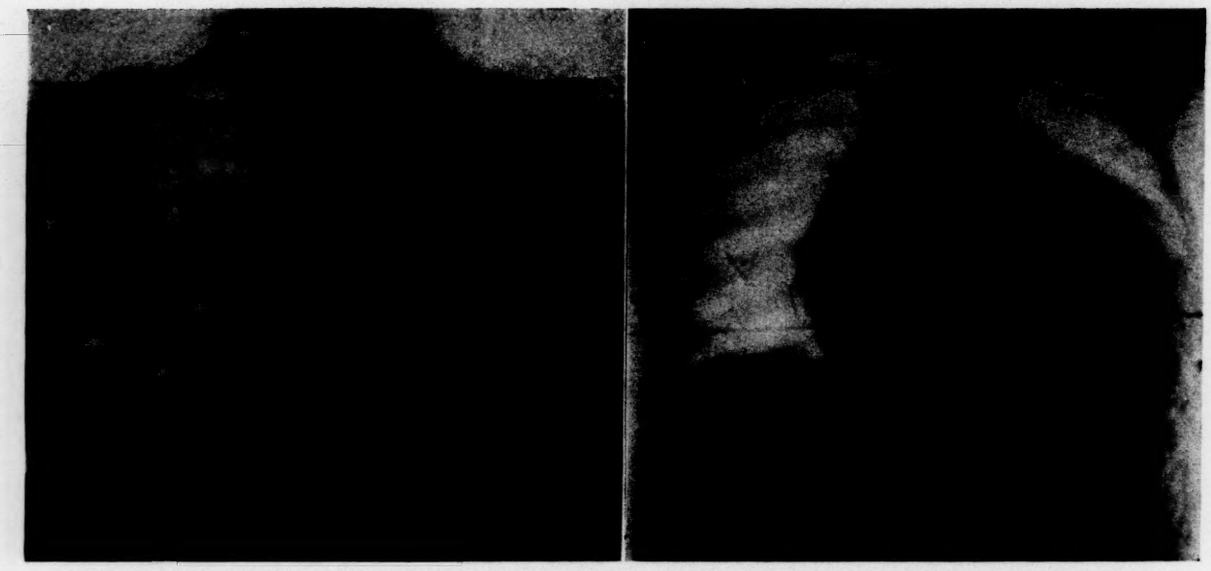


FIG. 5. Huge heart in pure pulmonary valvular stenosis in a child aged seven years. In the plain radiograph the dilated pulmonary artery is concealed by the huge heart but is revealed in the angiocardiogram.

indicative of right ventricular strain; right bundle branch block is also often seen.

Evidence of right-sided failure is often detected and in severe cases peripheral oedema and ascites may be present; the urine may contain albumen.

The disability varies but may be extreme; the patient may be able to walk only a few yards or may even be bedridden.

An important clinical feature is shown by attacks of loss of consciousness; these are of grave omen and usually presage another characteristic of this disease, sudden death.

Additional Investigations. The circulation times are usually prolonged, perhaps up to as much as thirty seconds. The presence of a shunt may be confirmed by an approximation of the arm-to-lung and arm-to-tongue times but both are still usually prolonged.

Angiocardiography confirms the very slow circulation in the more severe cases and also reveals an interatrial shunt if one is present. The post-stenotic dilatation of the pulmonary artery is emphasized (Fig. 4) or revealed (Fig. 5B); typically the contrast medium remains a very long time in the pulmonary artery, even after it has ceased to opacify the heart.

Cardiac catheterisation provides several pieces of information of diagnostic value. It may reveal or confirm the patency of the foramen ovale by passage of the catheter into the left atrium; it will demonstrate a rise of pressure in the right ventricle, often commensurate with the severity of the obstruction. Although in mild cases the rise may not be great, in severe cases it may be more than 200 mm. Hg systolic; a notable feature is that it is higher than the systemic pressure, indicating absence of an interventricular septal defect. The catheter may be held up at the valve level and as it passes an abrupt fall in pressure is seen, often to as low as 10 mm. Hg. If the orifice is small, the presence of the catheter may cause a marked drop in oxygen saturation of the pulmonary artery blood and may cause distress or collapse of the patient. The arterial oxygen saturation is diminished only if there is a right-to-left shunt. By the same token polycythemia may be present.

All grades of severity of this condition are seen at all ages. It may be found as a mild almost symptomless condition in a young adult; it may present as a grave illness with marked cyanosis and severe disability and with a huge heart in a child of a few years of age. (Fig. 5.) Apart from the subjective features, of great importance are the onset of cyanosis, enlargement of the heart (especially if progressive), venous congestion, electrocardiographic changes indicating strain especially in the chest leads and demonstration of a high right ventricular pressure at catheterisation.

Fallot's Tetralogy. Cyanosis and dyspnoea may be noted from birth but in a number of cases nothing abnormal is detected until the

child begins to move about. Cyanosis may be observed all the time or may be absent at rest and appear on exertion. Squatting is a common and important feature and its presence is strong evidence of Fallot's tetralogy. Clubbing is always present and varies with the degree of central cyanosis. Polycythemia is usually found, the red cell count sometimes being over 10,000,000 and the haemoglobin over 160 per cent with a haematocrit over 80 per cent. These very high figures are especially seen in cases with severe venous-arterial mixing and much cyanosis. Almost normal counts are sometimes seen, usually in cases in which the chief complaint is disability.

Most patients have their good days and bad days; extremes of heat or cold weather are more troublesome. Attacks of cyanosis or loss of consciousness are seen in the more severe cases and are of ill omen.

The prognosis is not good; many patients die young and Campbell in his clinic at Guy's Hospital has observed that one in two reaches the age of seven, one in five the age of fourteen and no more than one in ten the age of twenty-one.

The heart is not usually enlarged; a systolic thrill may be felt over the pulmonary outflow tract and a systolic murmur is heard over the same area. This murmur varies greatly in character and intensity; it may be soft and fairly localised, perhaps to the pulmonary area, or it may be loud and harsh, of "sawing wood" character, heard all over the precordium and conducted widely throughout both chests.

The electrocardiogram shows a right ventricular preponderance.

Radiologically the heart is typically sabot shaped, with a deep pulmonary bay; in about one in four cases the aorta is right sided. Screening confirms enlargement of the right ventricle. The most notable radiologic feature, for the significance of which we are indebted to Taussig, is the evidence of diminished blood flow to the lungs, as shown by clear lung fields and the absence of pulsation in the main pulmonary arteries. These are typically small but sometimes show some dilatation. The observation of increased vascular markings of the lungs and hilar pulsation is strongly against pulmonary stenosis.

Although a diagnosis can be made in most cases on the information briefly detailed previously, much more additional valuable information s obtained by angiocardiography and

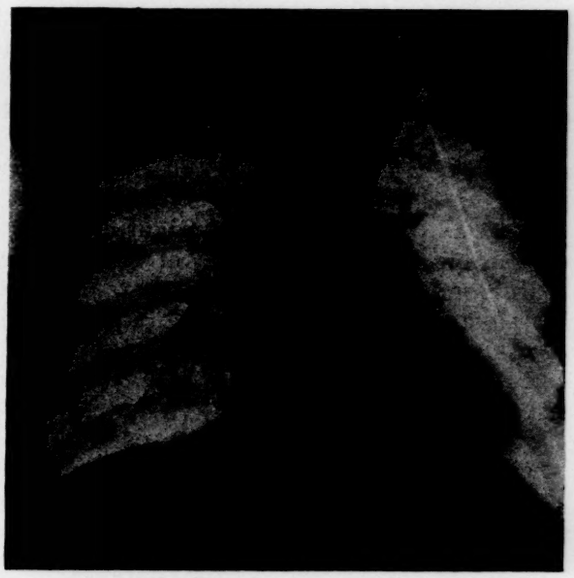


FIG. 6. Angiocardiogram in Fallot's tetralogy to show disposition of the main vessels and the presence of a valvular stenosis (note the globular swelling at the base of the pulmonary artery).

cardiac catheterisation. The first of these is especially helpful as, in addition to aiding in diagnosis, it enables the surgeon to study the pressure, size and length of the systemic arteries and whether the right and left pulmonary arteries are present. It may afford valuable information on the exact site and nature of the pulmonary stenosis (Fig. 6), especially if an infundibular chamber is shown. In this connection selective angiocardiography, in the lateral position with a catheter in the right ventricle, is especially helpful as it avoids superimposition of the shadow cast by the superior vena cava and right atrium.

Cardiac catheterisation can confirm the pulmonary stenosis by revealing a raised pressure in the right ventricle and the sudden drop in pressure distal to the stenosis so that the pressure is always low in the pulmonary artery in contrast to a number of other conditions (for example Eisenmenger's complex) in which it is normal or much raised. The catheter may reveal whether the change in pressure occurs at the valve level (valvular stenosis), below the valve level (infundibular) or if there is a double change due to a combined valvular and infundibular stenosis. The catheter by entering the aorta from the right ventricle will confirm an overriding aorta or dextroposition. As a result of the interventricular septal defect the right ventricular pressure in Fallot's tetralogy

is never more than the systemic pressure and indeed is rarely over 100 mm. Hg. This is in marked contrast to pulmonary valvular stenosis with a closed interventricular septum in which the pressure may be twice as much.

Although auscultation may help in diagnosing the level of the stenosis, it is more often of no help at all. A high systolic murmur conducted upward may be in favour of a valvular stenosis, and a murmur heard lower down, maximal over the fourth left interspace and of a harsh character, may favour an infundibular stenosis; but the latter type of murmur is often heard in valvular stenosis also.

Even with the information provided by angiocardiography and cardiac catheterisation the exact clinical diagnosis may be uncertain, as also may be the level of the pulmonary obstruction. In all cases the final diagnosis, especially the level and nature of the pulmonary stenosis, must await operative exposure of the heart, as will be detailed later.

A word of warning should be given about angiocardiography in the more severe cases, especially those deeply cyanosed or with a history of attacks of unconsciousness. These patients may die as a result of this examination and it is often wiser to dispense with it in this type unless it is essential.

Differential Diagnosis. A full account of differential diagnosis would involve writing a book and so only the most general points can be mentioned. The fundamental feature in cases of pulmonary valvular stenosis is demonstration and recognition of a diminished blood flow to the lungs which is observed radiologically and by catheterisation. Conditions with an increased flow, such as atrial septal defect, transposition of the great vessels, Eisenmenger's complex, interventricular septal defect and primary pulmonary hypertension should be readily excluded. The pulmonary second sound is loud in these conditions in contrast to the normal or quiet sound in pulmonary stenosis. The absence of a systolic thrill and murmur suggests a truncus arteriosus or pulmonary atresia; in these cases a continuous murmur may be heard from a patent ductus arteriosus or from enlarged bronchial arteries.

Tricuspid atresia is usually recognised fairly easily by left preponderance on the electrocardiogram; this is scarcely ever seen in any other variety of congenital cyanotic heart disease. These patients are commonly very blue and very disabled.

CHOICE OF OPERATION

Indications for Operation. Cyanosis and disability do not necessarily mean the patient is suitable for an operation. The essential feature, as already stated, is demonstration that the blood flow to the lungs is diminished. Once this has been shown to be so there is a strong *prima facie* case for operation except in those in whom disability and cyanosis are minimal. Even though cyanosis be slight, disability may be severe. The severity of the lesion is usually reflected in retardation of physical development. If symptoms are at all marked, operation should be advised as very few of these patients grow up to be useful citizens able to earn their own living.

Operation should be postponed if possible until four or five years of age unless the child is very ill and there is little chance of survival. The operation is more hazardous in infants; and if an anastomosis is used, it may be difficult to make an adequate stoma, although the aortic-pulmonary anastomosis of Potts can solve this problem. In general, also, patients in the middle or late twenties, or older, are much worse risks. The best age for operation in the Fallot group is four to fourteen years. An urgent indication for operation is worsening of symptoms, especially if associated with attacks of cyanosis or unconsciousness. It has been said that the worse the patient the more urgently is operation needed.

Pure pulmonary valvular stenosis should be considered somewhat differently from the Fallot group. Some cases are seen without symptoms, the heart is not markedly enlarged and the electrocardiogram shows no evidence of right ventricular strain. It is permissible to watch such cases but even in these it is safer to do a cardiac catheterisation to ensure that there is not a high systolic pressure in the right ventricle. If the right ventricular pressure is much raised, e.g. over 75 mm. Hg, then operation should be done irrespective of the absence of symptoms because later deterioration is inevitable and the risk of operation is increased.

Except for these mild cases of pulmonary valvular stenosis, valvulotomy should be advised in all; certainly if there is cyanosis and disability, cardiac enlargement, gross right ventricular hypertrophy, evidence of right-sided venous congestion and a raised intraventricular

pressure. A history of fainting attacks is especially dangerous.

My own policy is never to leave these patients waiting for operation once the decision has been made. Deterioration and death are always a grave danger in this disease and with any delay the patient may have passed from the phase of low risk and the prospect of a good result to that of grave risk and possible permanent cardiac damage.

Direct Versus Indirect Operations for Congenital Pulmonary Stenosis. Before the classic work of Taussig and Blalock these sufferers had no hope of relief. Taussig and Blalock's use of a systemic-pulmonary anastomosis gave them the prospect of great, even dramatic improvement, banishing cyanosis and disability. The contribution of Potts and his colleagues, by making an aortic-pulmonary anastomosis feasible, was another great help.

The brilliant success of these anastomotic operations, however, must not blind us to certain potential inherent drawbacks. The effect of the anastomosis is to by-pass the pulmonary stenosis; to lead back into the pulmonary artery unoxygenated blood that has escaped from the right ventricle into the aorta. Nothing is done to relieve the intracardiac obstruction directly, and, in fact, the creation of an artificial ductus arteriosus in effect contributes yet another abnormality to an already complicated cardiac abnormality; a naturally occurring patent ductus arteriosus is ordinarily closed by an operation. It may be argued, and probably with a considerable degree of justification, that the mechanical state of affairs after a Blalock or Potts operation is not strictly comparable with that seen in a natural patent ductus arteriosus. In the natural condition there is an increased blood flow to the lungs and the heart has to perform a continuous and unnecessary extra amount of work owing to the arteriovenous leak. In pulmonary stenosis the pulmonary blood flow is diminished and the object of the artificial ductus is to increase this to nearer normal.

There is, however, another important aspect to be considered. The effect of the daily wear and tear of the blood stream forcing its way past the pulmonary stenosis is to cause a steady worsening of it as a result of the deposition of platelets and fibrin on its surface, leading to fibrosis and contracture, and in older patients to the growth of warty vegetations and even calcification. Ultimately, if the patient lives long enough, the pulmonary stenosis becomes entirely or virtually impassable; in other words a condition of acquired pulmonary atresia develops. Many patients die before this phase but if life is prolonged by an anastomotic operation it is likely that many will come to it. The condition is then comparable to that seen in truncus arteriosus in which there is complete intracardiac mixing and blood reaches the lungs only by the artificial ductus or by other anastomotic channels, scarcely a state of affairs conducive to a long and trouble-free life.

These objections to the indirect operations could be avoided by a direct operation on the pulmonary stenosis for its relief. The advantages would be several. The basic heart lesion is rendered more nearly normal instead of more complex. The arteriovenous leak is avoided. Moreover, the venous-arterial leak within the heart (right ventricle to aorta, or right atrium to left atrium) is lessened; as blood can now pursue its normal course into the pulmonary artery less will be directed along the abnormal channel. Cyanosis and disability will be relieved by the dual mechanism of increasing the pulmonary blood flow and diminishing the venous-arterial shunt.

It has now been abundantly shown that direct operation upon the pulmonary stenosis is practicable, reasonably safe and gives immediate results as good as those of the indirect procedures.

It is not possible at this time to say which will prove to give the better long term results; time alone can tell this. It will be no discredit to either method if one or other is shown ultimately to be inferior. Surgery is not static; it must evolve and expand by trial and error. Only by testing out these two policies of indirect and direct attack can we decide which is the better. A problem in surgery is being presented and faced and a sincere attempt is being made to solve it. Obviously it is correct for surgeons to practice either or both methods until the final answer is revealed.

The objections put forward to the direct operations have been several. First, that they are neither feasible nor safe; this has already been shown to be incorrect. A much more real objection is that the relief of the pulmonary stenosis will mean that the increased intraventricular pressure will be transmitted to the lung vessels and a condition resembling Eisen-

menger's complex will develop. Up to now we have observed nothing to support this; many pressure records have been taken at operation after division or resection of the stenosis and in no case has an intrapulmonary pressure higher than normal been recorded. This may be due to the fact that sufficient stenosis remains to spare the lung circulation but I doubt if this is so as in most cases of pulmonary valvulotomy, at any rate, a very large passage is formed. The probable explanation is that the blood flow can be increased without a pressure rise; the pulmonary vessels can easily relax to compensate for any rise of pressure. More accurate information will be provided by late catheterisation studies but so far we have not been able to amass sufficient data to furnish a full report; so far no case of secondary pulmonary hypertension has been observed.

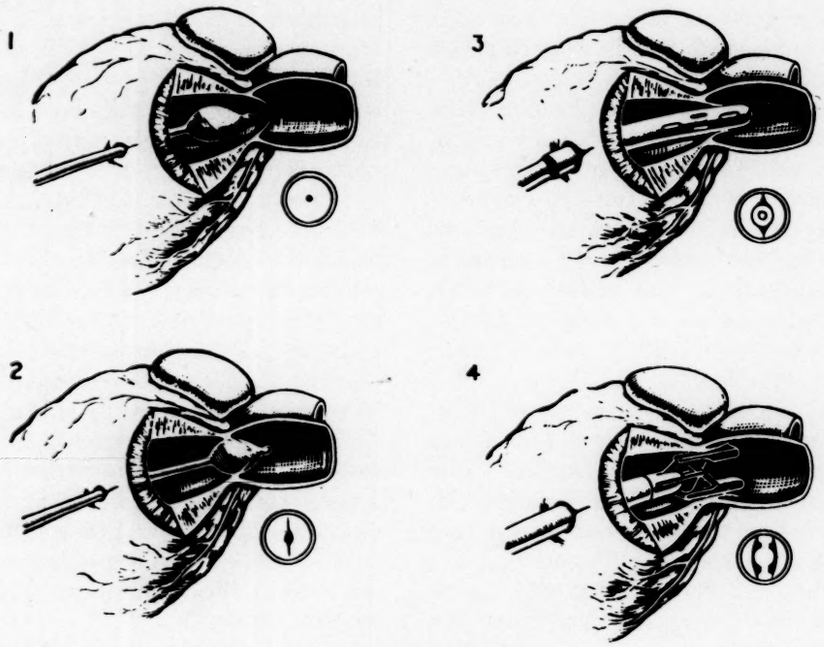


FIG. 7. Technic of valvulotomy.

Whatever may be the correct treatment in lesions of the Fallot type, there can be no question about the treatment of pulmonary valvular stenosis with a closed interventricular septum; a pulmonary valvulotomy must be done. An anastomosis does nothing to relieve the strain on the obstructed right ventricle but merely throws an added strain on the left ventricle. The already labouring right circulation is further impeded by the additional systemic flow into the lungs. The inevitable result is the development of right-sided failure that may come on immediately after the operation. In the early days of the Blalock and Potts procedures, before the significance and indeed common occurrence of pure pulmonary valvular stenosis was recognised, a number of these cases were submitted to an anastomosis with unfortunate results. The only way to retrieve the situation is to perform a pulmonary valvulotomy and close the anastomosis. I have had to do this in several cases.

It is now generally accepted that valvulotomy is the only operation to be used in the treatment of pulmonary stenosis with a closed interventricular septum (Brock 1948, 1949, Brock and Campbell 1950*a*, Blalock 1950, Potts 1950).

Pulmonary Valvulotomy for "Pure" Pulmonary Valvular Stenosis. Although it is possible to approach the pulmonary valve through the pulmonary artery in a retrograde manner (Brock, 1950), in general it is preferable to approach it through the right ventricle. The operation, as will be seen from later figures, is very well borne provided it is not delayed until the patient is worn out, with a grossly enlarged heart or even in heart failure. If valvulotomy is performed before this gross deterioration, the mortality is no higher than that of any other major intrathoracic procedure.

Anaesthesia must be perfect and adequate

oxygenation is imperative. In the earlier days before we routinely used intravenous procaine hydrochloride or procaine amide, the heart would react violently to interference by various arrhythmias; now these are rarely seen. We have noticed no definite advantage in procaine amide over procaine hydrochloride; indeed I have had ventricular fibrillation develop when the amide was being used and have corrected it with the hydrochloride.

I prefer an incision through the third left interspace, usually with division of the third and sometimes the fourth costal cartilage. The hypertrophy of the right ventricle results in this presenting freely into the operative field; the effect of the hypertrophy is also to push the pulmonary artery upward and backward, hence the high approach through the third interspace is needed.

Before opening the pericardium 5 ml. 0.25 per cent decicaine (amethocaine, pontocaine) are instilled into it. Strong solutions of procaine give poor surface anaesthesia and cause a severe, often delayed, chemical pericarditis. The decicaine, which is absorbed or neutralised within two minutes, gives good local anaesthesia and diminishes surface irritability which otherwise may be dangerous in severe cases. Procaine 0.5 per cent is always injected into the wall of the ventricle at the site of incision.

The steps of the valvulotomy are shown in Figure 7; a special valvulotome is introduced and cuts the valve across its diameter; this opening is enlarged by bougies and an expanding dilator so that the valve diaphragm splits completely across to give two functioning flaps. (Fig. 8.) In this way regurgitation is prevented. Haemorrhage is controlled by simple finger pressure and sutures can be passed under the controlling finger and then tied. Blood loss is usually not great.

The author has operated upon forty-three patients with pure pulmonary valvular stenosis; nine of these died but in four death occurred before the heart was touched and in one case during induction of anaesthesia. These were all late severe cases; they died, not because of a direct operation upon the heart, but because they were bad cases. Excluding these there were five deaths among thirty-nine patients in whom valvulotomy was done; two of these had previously had a Blalock operation performed and both were in heart failure. It will thus be seen

FIG. 8. Appearance of pulmonary valve after valvulotomy.

that the mortality of the operation need not be high. The results are good; one patient delivered herself naturally of a baby eleven months after operation. Another underwent valvulotomy during the fifth month of pregnancy which proceeded and terminated normally.

Pulmonary Valvulotomy in Fallot's Tetralogy. There is not the same absolute need for a direct operation on the stenosis in Fallot's tetralogy because the presence of an interventricular septal defect and an overriding aorta spares the right side of the heart. It was shown earlier that a valvular stenosis is common enough in Fallot's tetralogy to make valvulotomy a procedure of practical importance in treatment of the condition if the need for direct relief of the stenosis is accepted.

I have performed the operation thirty-nine times, with three deaths; two of the deaths occurred in adults. The result has been fair in seven and good or excellent in twenty-nine.

Combined Figures for Pulmonary Valvulotomy. The total number of patients who underwent pulmonary valvulotomy is eighty-two: thirty-nine of Fallot type, forty-three with pure valvular stenosis. Twelve patients died, an over-all mortality of some 13 per cent but this includes the early pioneer period when patients who were bad cases were being operated upon. Thus nine deaths occurred in the first twenty-one cases and only three in the last sixty-one (5 per cent).

Infundibular Resection. In the rare cases of isolated infundibular stenosis with closed septa, a direct operation for relief of the obstruction is just as imperative as in pulmonary valvular stenosis with closed septa; an anastomosis must

not be used. In the ordinary Fallot type a direct operation on the infundibular stenosis is not essential but its advantages have been detailed.

The morbid anatomy of infundibular stenosis was described earlier and emphasis made of the fact that the obstruction is confined essentially to one level within the infundibulum which, although generally smaller than normal, has otherwise an effective lumen, except in some cases in which the whole infundibulum is severely hypoplastic. This last type demands an anastomosis but in all the others, if the local maximal obstruction is relieved by operation, the outflow channel is then adequate.

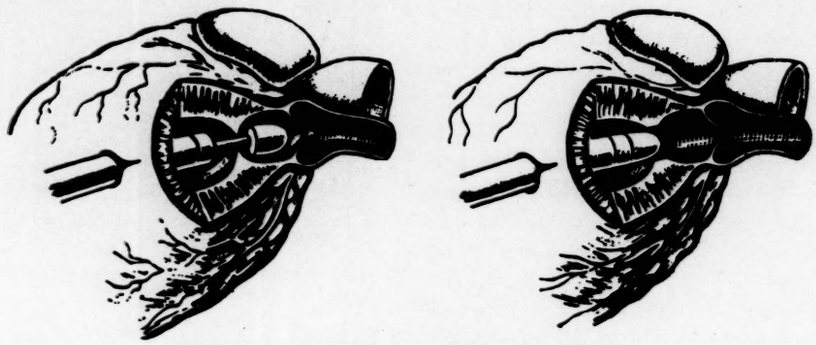


FIG. 9. Technic of infundibular resection.

Infundibular resection can be effectively performed by insertion of a special punch through an incision in the wall of the right ventricle. (Fig. 9.) In Figure 10 portions of tissue removed in this way showing the thickened endocardium of the stenosis can be seen.

In some cases in which the stricture is very resilient, actual resection may be difficult but in these cases excellent results have followed simple dilatation (Brock and Campbell 1950*b*).

When the stenosis is high, immediately below the pulmonary valves, there is clearly the added risk of damage to the valve cusps. For this reason an anastomosis may be preferred in some cases of high infundibular stenosis. Certainly in adults (over twenty years) I do not attempt resection of a high infundibular stenosis because there is too much fibrosis and dense contracture and it is difficult to enlarge the passage effectively. In these patients the infundibulum has been tethered and prevented from growing because of the fibrous barrier; indeed the daily wear and tear has been followed with increasing fibrosis and narrowing. An added advantage of infundibular resection in children is that, by releasing the infundibulum from the tethering action of the stenosed ring, it is enabled to grow and develop, especially under the influence of the larger flow of blood.

If a valvular stenosis co-exists, valvulotomy may be performed at the same time.

I have performed infundibular resection in thirty-nine cases with seven deaths; there have been no deaths in the last twenty-six cases. In ten cases infundibular resection has been combined with valvulotomy, with no deaths. In four cases the result has been fair or poor; in the remaining twenty-eight it has been good or excellent.

The Policy of Direct Exploration of the Pulmonary Stenosis. It was mentioned earlier that if an indirect operation is used, it is common for the surgeon to open the chest, free the relevant vessels and perform the anastomosis, and to close the chest without achieving any greater accuracy in or confirmation of diagnosis. Certainly if a right-sided approach is used, the heart cannot be examined.

My own policy is to strive to achieve accuracy in diagnosis in all cases by supplementing the preoperative examinations and investigations by careful exploration of the heart at thoracotomy. Modern cardiology does not finish with angiocardiography and cardiac catheterisation; it is carried into the operating theatre when the heart is exposed and examined directly and critically. Only in this way can a high standard in diagnosis be obtained and the correct type of operation chosen.

For this reason I prefer to use a long, left lateral thoracotomy incision which can be extended backward or forward as may be desired and which allows performance of a direct heart operation or of a Blalock or Potts anastomosis after a decision has been made.

The pericardium is opened in all cases and the external features of the heart and pulmonary artery inspected. Familiarity with the appear-

FIG. 10. Portions of tissue removed from the infundibular stenosis.

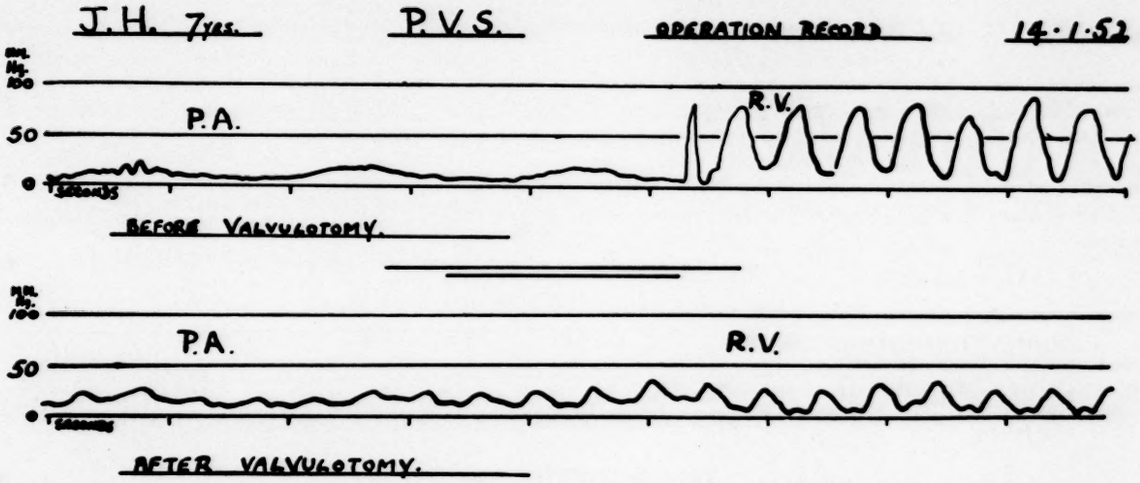


FIG. 11. Direct intracardiac pressure records taken at operation to show pulmonary valvular stenosis before and after division of the valve.

ance of the various conditions will usually enable an accurate diagnosis to be made; it is not possible in this article to detail all the diagnostic criteria. In order, however, to confirm and amplify the observations direct pressure readings are taken on an electromanometer, either by needle puncture of the ventricle, infundibular chamber and pulmonary artery or, preferably, by introduction of a catheter through a small incision in the ventricle. In this way a high standard of diagnosis is reached; the abrupt nature of the stenosis is demonstrated. (Figs. 11 and 12.) The occurrence of a combined valvular and infundibular stenosis is revealed and the relative importance of the two can be assessed. (Fig. 13.) Pressure records can again be made after the stenosis has been relieved. I will not now operate on a case of pulmonary stenosis without having catheters and an electromanometer available in this way.

Selection of a Direct or an Indirect Operation. The choice between a direct and an indirect operation is, of course, confined to the Fallot group of cases in which there is an interventricular septal defect. When the septum is closed, a direct operation must be done.

The policy of a direct attack on the pulmonary stenosis was not decided upon and followed at once in all cases. Before embarking routinely upon such a radical change it was necessary to expand slowly feeling one's way, as it were, in the new technique and selecting suitable cases and rejecting less certain ones until increasing experience, skill and knowledge enabled the direct operation to be used more often. For this reason the proportion of direct to indirect operations has been steadily altering from the initial routine anastomosis some four to five years ago to the present state when an anastomosis is usually not performed unless there is no alternative. Presumably some such gradual progressive evolution of policy will be adopted by other surgeons wishing to follow the direct procedures.

I use an anastomosis in all cases of tricuspid atresia and in most cases of pulmonary atresia.

Pulmonary Arteries | Infundibulum Right Ventricle | Body of Right Ventricle

Before Operation

FIG. 12. Patient F. C., July 25, 1951. Direct intracardiac pressure records taken at operation to show infundibular stenosis.

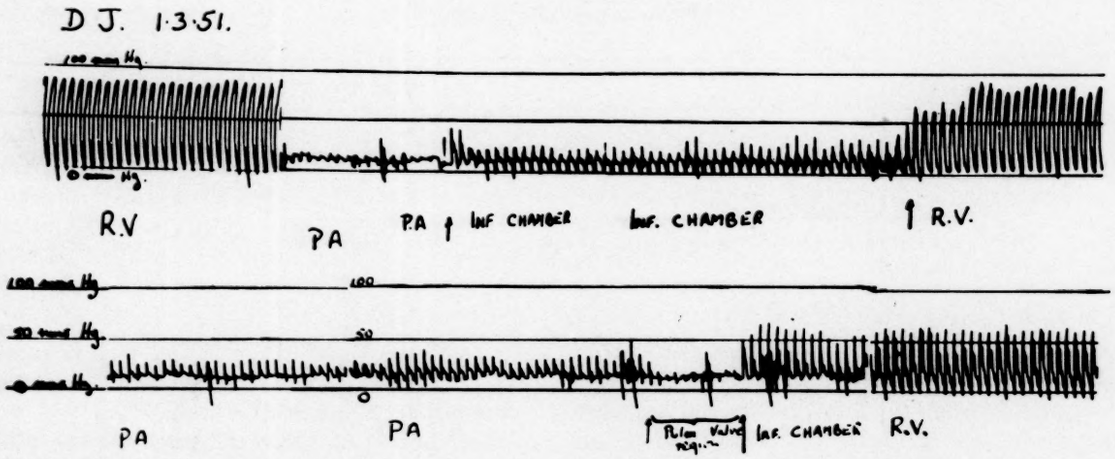


FIG. 13. Direct intracardiac pressure records to show combined valvular and infundibular resection and valvulotomy.

In two cases of pulmonary atresia in which the atresic process was at the valve level a direct operation was possible, with excellent results.

Valvulotomy is always done if a valvular stenosis is diagnosed; in general today I do an infundibular resection when an infundibular stenosis is recognized, except in certain cases of *high* infundibular stenosis. Occasionally the presence of large tortuous coronary vessels covering the anterior surface of the right ventricle over the area needed for the cardiotomy may compel the use of an anastomosis. Actually I have not used an anastomosis during the last six months on any patient except in tricuspid or pulmonary atresia.

Comparative Figures of Direct and Indirect Operation. The progressive change of policy in regard to the use of a direct or an indirect operation is seen in the comparative figures for the two groups of operations over the last four and a half to five years.

Of a total of 240 cases of congenital pulmonary stenosis operated upon, exploratory thoracotomy only was done in seventeen, either due to an error in diagnosis or inability to perform any useful operation. The remaining 223 cases were dealt with as follows: anastomosis, 112 and direct operation, 111. In eight cases anastomosis was used because of tricuspid or pulmonary atresia. In the first fifty cases (May, 1947 to October, 1948) the proportions were as follows: direct operation, six and anastomosis, forty-four. In the last fifty cases (February, 1951 to

January, 1952) the figures were: direct operation, forty-one and anastomosis, nine.

It will be seen that the transition from use of an anastomosis in almost all cases to its rejection in all but unavoidable cases is virtually complete and has taken about four years. The change of practice has not been made suddenly or without the support of knowledge and experience. It now remains to continue to use the direct operations and to observe the long term results so that the late prognosis of the two methods may be assessed and compared. Only in this way can a final decision be made on the comparative merits of the two procedures.

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Combined Staff Clinic

Chemotherapy of Cancer

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Gilbert H. Mudge.

DR. ALFRED GELLHORN: Over the past half century we have had the opportunity to assess the results of cancer treatment by the conventional methods of surgery and radiotherapy. The conclusion must be reached that additional means of treatment are still necessary and for this reason there has been a resurgence of interest in the chemotherapeutic approach to malignant disease. In addition, the dramatic successes achieved by antibacterial chemotherapy have provided a striking stimulus to the hope that drugs could be found which would selectively destroy neoplastic cells.

Sober reflection, however, quickly leads to the realization that there are certain fundamental differences between the chemical treatment of infections and cancer which make the problem of cancer chemotherapy extremely difficult. In antibacterial chemotherapy the offending invader is foreign to the body and innate defense mechanisms are mobilized which supplement and complement the action of antibacterial drugs. In the case of the malignant cell, however, no qualitative differences have been found between it and the normal cells of the body and there is no convincing evidence that defense mechanisms are mobilized to combat the invasion of malignant cells. This qualitative similarity between the normal and the neoplastic cell led one distinguished investigator, who had devoted almost an entire lifetime to the search for possible drugs to destroy the neoplastic cell, to state that finding a drug to cure cancer is like finding a drug which will dissolve away the left ear without harming the right ear.

Last year in a clinic devoted to this subject we reviewed the current status of clinical cancer chemotherapy. You will recall that there was a discussion of androgen control therapy of prostatic carcinoma in which it was demonstrated that castration in combination with the administration of estrogens led to general improvement and increased duration of life in patients suffering from disseminated prostatic carcinoma, and that there was relief of pain and decrease in size of the soft tissue metastases. Brief mention was also made of the fact that androgen and estrogens have found a place in the palliation of metastatic carcinoma of the female breast; the indication was, and I believe still is, that this is a non-specific action although the patient frequently receives significant if temporary benefit. It was also indicated that ACTH and cortisone have a place in causing remissions in acute leukemia, particularly in childhood, and have a limited application in the management of certain lymphomas; that urethane may be used as a substitute for radiotherapy in the treatment of chronic leukemias and also has application in the management of multiple myeloma; that the nitrogen mustards play a role in the treatment of patients with malignant lymphomas, certain blood dyscrasias and bronchogenic carcinoma; and that the folic acid analogues are useful in the treatment of acute leukemia, particularly in childhood.

The plan today is to continue the discussion initiated one year ago. Today, however, our attention will be focused on the mechanism of action of a few of these drugs and of a chemical compound which is now being studied in the laboratory. Our objective will be to assess what we have learned from these drugs in terms of the biology of malignant disease and to look into possible future developments.

In our discussion nucleic acids will figure prominently and, therefore, to provide the proper setting for an understanding of the future discussions, Dr. Chargaff will review certain pertinent aspects of nucleic acid metabolism.

DR. ERWIN CHARGAFF: Nucleic acids are essentially high molecular compounds consisting of a group of nitrogenous components,

of sugars and of phosphoric acid. We distinguish two main types, the so-called desoxypentose nucleic acids and the pentose nucleic acids; as the names imply, the main differentiation which we make lies in the type of sugar that these nucleic acids contain. The desoxypentose nucleic acids seem, at least in the mammalian cell, to be limited entirely or in large part to the nucleus.

It is not inconceivable, although there is no clear-cut evidence about it, that certain cells, especially those with a large cytoplasm and relatively small nuclei as we find for instance in the eggs of the invertebrates, do contain desoxypentose nucleic acids in the cytoplasm in a diffuse form, not demonstrable histologically. The pentose nucleic acids are found mainly in the cytoplasm of the cell in certain structural, well recognizable elements such as the mitochondria, and also in the submicroscopic particles. The nucleus also is known to contain pentose nucleic acids in the distinct structure known as the nucleolus. In general, then, we can consider pentose nucleic acids chiefly as components of the cytoplasm and desoxynucleic acids as components of the nucleus.

What have pentose and desoxypentose nucleic acids in common? Most desoxypentose nucleic acids and pentose nucleic acids contain the same purines, adenine and guanine. In the desoxypentose nucleic acids the pyrimidines found are mainly cytosine and thymine; in the pentose nucleic acids thymine is replaced by uracil. Very recently, evidence has been brought forward to show that a third pyrimidine also plays a role in certain desoxypentose nucleic acids of mammalian and plant cells, namely, 5-methylcytosine. Desoxypentose and pentose nucleic acids have one other important feature in common. They have more or less the same absorption spectrum in the ultraviolet, exhibiting extremely sharp and high peaks around 260 mμ.

Wherein do these two types of nucleic acids differ? As already mentioned they contain at least one different pyrimidine, thymine in desoxypentose and uracil in pentose nucleic acids, and also different sugars. In all desoxypentose nucleic acids so far examined only one sugar has been found, namely, 2-desoxyribose. All pentose nucleic acids so far examined have yielded only one type of sugar, namely, ribose. Desoxyribonucleic acids are extremely fibrous asymmetric structures which endow solutions with a very high degree of structural viscosity. Pentose nucleic acids, on the other hand, seem to be spherical in shape and their solutions have no considerable viscosity. The desoxypentose nucleic acids in general are assumed to consist of a very long chain of nucleotides. The ribonucleic acids, on the other hand, have been shown to be very rich in side branches. We have in one case something like an eel and in the other something like a hedgehog. Whether these different physical shapes have anything to do with the particular biologic properties of the nucleic acids cannot now be said; but we should not forget that the nucleic acids in the cell do not occur in the free state or as salts. They occur in protein linkage as conjugated proteins.

If we compare the nucleoproteins of the two types mentioned, we find certain distinct differences. The desoxypentose nucleoproteins of the nucleus are relatively easy to dissociate. In many cases it is sufficient to dissolve such a nucleoprotein in strong salt solution to liberate the free desoxypentose nucleic acid. This is even more characteristic of sperm nucleoproteins which contain compounds of nucleic acids and basic proteins of the protamine type. On the other hand the pentose nucleoproteins of the cytoplasm, as exemplified in the structures mentioned before, namely, mitochondria or microsomes or submicroscopic particles, are extremely difficult to dissociate. It is necessary to break down the protein, usually by proteolytic digestion or in a similar way, to liberate the nucleic acids.

What can be said about the biologic significance of nucleic acids? First of all it is safe to state that there is no living cell, no completely autonomous living system, which does not contain both types of nucleic acid, desoxypentose and pentose nucleic acids. One might object that I have forgotten the viruses, because viruses have often been found to contain only one type of nucleic acid. For example the plant viruses of the tobacco mosaic type are essentially pentose nucleoproteins and many animal and bacterial viruses of the phage type have been shown to be desoxypentose nucleoprotein exclusively. However, we should not forget that a virus is, by definition, only one-half of a living structure. It has to impose itself upon the nucleus or cytoplasm to induce reproduction of the virus. For this reason it is still safe to say that both desoxypentose and pentose nucleic acids are necessary for life.

Second, desoxypentose nucleic acids have been shown to be active agents in the transformation of certain bacterial types. In this case the present evidence is quite good that we are dealing with a naked desoxypentose nucleic acid and not with a nucleoprotein, although one still has to reserve judgment. We must assume that such bacterial types as pneumococcus or hemophilus possess a mechanism enabling the material to enter the cell and induce a transformation or mutation.

Third, when we examine the efficiency of ultraviolet radiations of different wavelengths to produce mutations, it will be found that the mutagenic activity spectrum coincides quite closely with the characteristic absorption spectrum of a nucleic acid. This would seem to bring into direct relationship the chemistry of nucleic acids and the chemistry of mutations.

Fourth, it has been shown that within the same species the amount of desoxypentose nucleic acid per diploid nucleus is constant. Of course, like all these generalizations, this statement must be accepted with great caution, but at present this seems to be true. If we go from a diploid nucleus of the same species to a haploid nucleus such as is found in the sperm cell, we find almost exactly half the amount of desoxynucleic acid; so far this seems to be the really constant element in the nucleus of a given species. Furthermore it could be shown in a number of cases that the desoxypentose nucleic acids differ in composition from species to species in a characteristic manner but that they do not differ within different tissues of the same species. This finding also reminds us of certain concepts in genic specificity.

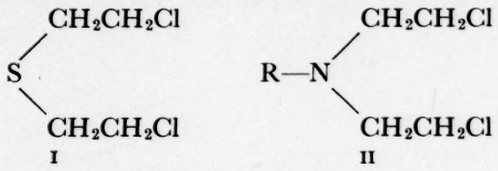
Furthermore if we go up the scale from the sperm cell to the highly differentiated cell of the same organism, we find that desoxypentose nucleic acid is the only element which does not change in its composition, that is, in its purine-pyrimidine ratio and certain other characteristics. The proteins undergo drastic changes from relatively simple structures, the protamines, to histones and even more complicated proteins. Since the desoxypentose nucleic acid component does not seem to change in composition, it is therefore presumably safe to conclude that desoxypentose nucleic acids are an important part of the chromosomes. Whether they are the only directing part of the genes cannot be said.

We do not know how many different nucleic acids are present in the nucleus of a given species. Assuming that each nucleic acid corresponds to one gene, we would have to conclude that if there were 10,000 different genes in the cell, there would be 10,000 different desoxynucleic acids present as separate entities. When you deal with a system which contains 10,000 constituents you might as well consider it as a whole. There is no method I know of which would permit us to separate something like 1,000 or 10,000 different nucleic acids from one another. The question whether we are dealing with one nucleic acid or with very many of similar kinds in the same cell must be left open for the present.

DR. GELLHORN: Let us turn our attention now to a group of cytotoxic chemical agents which are of interest in clinical cancer chemotherapy. Most of us have had personal experience with the nitrogen mustards and are familiar with the dramatic effects which they can produce in certain neoplastic diseases. We all know that patients with disseminated Hodgkin's disease may, within a matter of days after the administration of intravenous nitrogen mustard, have a drop in their temperature to normal levels, a gradual decrease in the infiltration of liver and spleen, and decrease in lymphadenopathy, all associated with marked subjective improvement and gain in weight. One cannot deny that this drug has an effect on neoplastic cells. At the same time we are also all familiar with the reactions that occur in patients to whom we have administered nitrogen mustards: the striking nausea and vomiting and the progressive drop in the white count and platelet count with attendant complications. Therefore, we have an agent which presumably strikes at fundamental mechanisms of normal as well as neoplastic cells. The question is how does this occur? I have asked Dr. Fred Philips, who is Director of the Pharmacology Section at the Sloan-Kettering Institute and who has had a large experience in the study of nitrogen mustards both during the war and afterwards, to tell us about this.

DR. FRED PHILIPS: As Dr. Gellhorn has indicated the initial interest in nitrogen mustards arose as the result of their potential usefulness as war gases. During the first World War sulfur mustard (1) had proved an effective weapon inasmuch as it is an oily, volatile, persistent substance with high capacity to produce necrosis in any directly contaminated tissue.

Between the two World Wars nitrogen analogues (II) were synthesized and found to be, like sulfur mustard, oily, volatile, vesicating



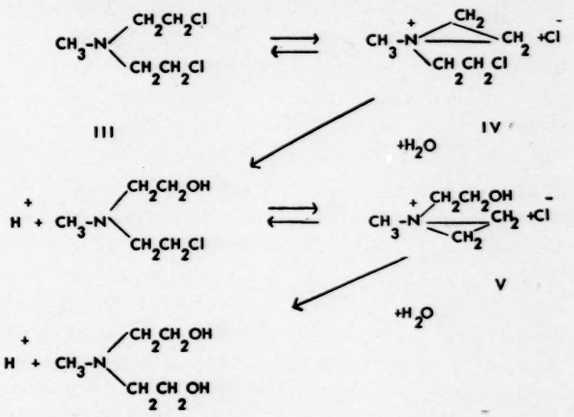
I II

agents. These came to be known as nitrogen or amine mustards because of obvious similarities to sulfur mustard in structure and properties. Their martial value appears of little import at present and hardly to be compared in interest with their more profound biologic actions.

The nitrogen mustards are tertiary amines containing two or three 2-chloroethyl groups. Fortunately the base strength of the amines is sufficiently great to permit their isolation as water soluble hydrochlorides. In this state they may be directly administered into the circulation without danger of contact injury to tissues. When so given in therapeutic dosage their effects are found to resemble closely those of whole body irradiation. It was, indeed, this radiation-like activity which sponsored the initial trials of the drugs in the treatment of human lymphoma.

Some understanding has been gained of the relation between the chemical properties of amine mustards and their biologic actions. In aqueous media of physiologic composition nitrogen mustards are unstable and transform rapidly into highly reactive ethylenimonium derivatives. It is reasonably certain that this process occurs *in vivo* and its nature is depicted in Figure 1 in the case of the drug, HN2 (III) or mechlorethamine (methyl-*bis*(2-chloroethyl) amine). During the course of transformation two ethylenimonium cations are formed successively. The first, methyl-2-chloroethyl-ethylenimonium (IV), is referred to as the chlorimine of HN2; the second, methyl-2-hydroxyethyl-ethylenimonium (V), is referred to as the hydroxyimine.

The complex and diverse pharmacologic effects of HN2 become comprehensible with reference to the aforementioned process of transformation. When given in acute, supralethal doses HN2 elicits stimulation of the central nervous system (convulsions), parasympathomimetic effects and a delayed neurologic disorder causing paralysis of skeletal musculature. It has been possible to relate the origin of each of these pharmacologic effects to either HN2 or its individual ethylenimonium transformations. Thus convulsions are caused only by the parent amine. Parasympathomimetic activity, that is, stimulation of autonomic ganglia and parasympathetic effectors and stimulation and depression of the myoneural junction, has been associated with



III IV V

FIG. 1. Transformation of HN2 in dilute aqueous solutions.

the formation *in vivo* of chlorimine (IV) while the delayed neurologic disorder appears to arise from *in vivo* formation of hydroxyimine (V). It is of interest to note in passing that parasympathomimetic properties of chlorimine have been related to resemblance of its molecular configuration to that of acetylcholine.

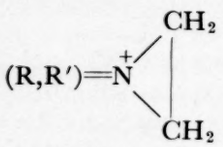
When median lethal doses of HN2 or chlorimine are given to mammals, a delayed lethal syndrome is manifested the nature of which is poorly understood and will not be discussed here. Simultaneously these same doses cause damage in many proliferating tissues. Thus necrosis and atrophy occur in all hematopoietic organs with the result that leukopenia, reticulocytopenia and thrombocytopenia develop as prominent features of intoxication. Intestinal epithelium is severely damaged, a finding associated with the persistent watery, often hemorrhagic diarrhea noted in delayed fatalities. Inhibition of spermatogenesis in testis and of cell division in corneal epithelium is also evident.

The administration of therapeutic doses of HN_2, as you know, causes transient regression of many lymphomatous tissues. Simultaneously hematopoietic organs sustain an extensive damage which, fortunately, is transient and reparable by virtue of the regenerative capacity of these organs. By the same token tumor regression is also transient; nitrogen mustards are, therefore, not curative agents. Nor can nitrogen

mustards, in the light of their known properties, be considered to exhibit specific carcinolytic actions. Rather the susceptibility of tumors must be viewed as akin to the sensitivity of proliferating tissues in general.

The foregoing presentation of the pharmacologic properties of HN_2 permits a definition of mustard-like activity in mammals. Thus mustards may be considered to be agents which in median lethal doses cause induction of a characteristic delayed lethal syndrome in association with extensive lesions in all hematopoietic tissues, in the epithelium of the entire intestinal tract and in other proliferating tissues. Furthermore cellular damage is confined solely to proliferative tissues. It is significant to note that a similar definition of pharmacologic properties might be offered to describe the actions of generalized irradiation with roentgen or other penetrating radiations.

Agents which elicit mustard-like actions in mammals appear, for the most part, to be molecules containing at least two reactive groups. In the case of nitrogen or sulfur mustards the reactive groups are 2-haloethyl radicals bonded, respectively, to nitrogen or sulfur atoms. As explained previously such groups are transformed *in vivo* into reactive ethylenonium



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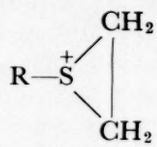
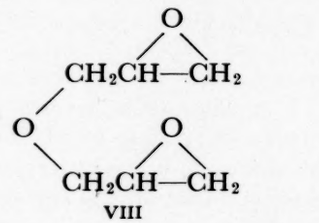
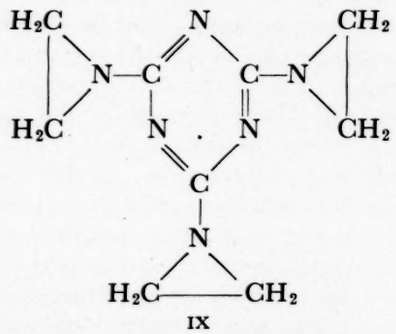


VII

moieties (VI and VII). These in turn engage in alkylating reactions which will be discussed herein. Other reactive groups have recently been found to endow molecules with mustard-like properties. These include ethylenepoxy and ethylenimino configurations found, respectively, in such substances as VIII and IX. Indeed IX, known as triethylene melamine or TEM, has been found therapeutically useful in the same neoplastic diseases of humans which respond to treatment with HN_2.

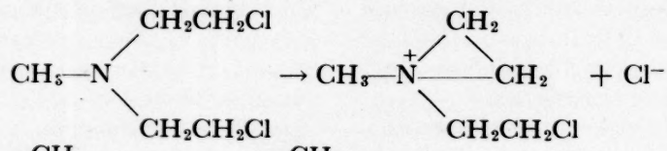


VIII

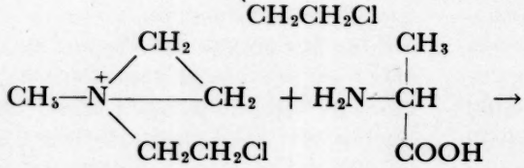


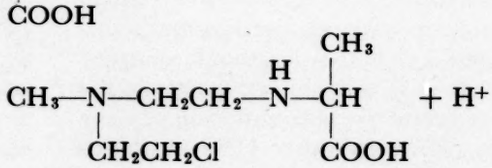
IX

Considerable effort has been directed toward elucidation of the mechanism of action of nitrogen mustards. Such agents are known to react readily *in vitro* with various compounds of biochemical importance. The manner by which such interactions take place is shown in the reaction between the amino acid, alanine, and HN_2. The process involves a two-step displacement. In the initial step (1) the parent compound is transformed into a reactive intermediate; the latter then reacts with the amino group of alanine (2) to give rise to an alkylated derivative of the amino acid. Similar reactions are known



(1)





(2)

to occur with many inorganic ions and with most radicals of biochemical importance such as carboxyl, α and ϵ-amino, imidazolyl, sulfhydryl, thio-ether, phenolic hydroxyl and organic phosphate. Accordingly the transformation products can alkylate such diverse biochemical entities as amino acids, peptides, purines, purine nucleosides and nucleotides, hexose and triose phosphates, and the vitamins, pyridoxine, thiamine and nicotinic acid. They also combine with more complex entities such as proteins and nucleic acids. In proteins condensation occurs most abundantly with carboxyl groups but also to a significant extent with free amino and sulfhydryl radicals. In nucleic acids interaction occurs primarily with phosphate and amino groups.

It is obvious that the propensity of the mustards for alkylation of biochemical entities *in vitro* is almost universal. Accordingly it is reasonable to assume cytotoxic activity to result from the interaction of amine mustards *in vivo* with vital loci in susceptible cells. By the same token, however, the lack of specificity of the alkylating reactions *in vitro* has retarded elucidation of the primary locus of chemical attack *in vivo*. For the latter purpose it is necessary to consider further the biologic properties of mustards.

Studies of the susceptibility of various biologic processes to mustard treatment have revealed mitosis to be, with few exceptions, the cellular activity most sensitive to disturbance. This has been verified with dividing cells obtained from widely varying plant and animal species. An excellent example of the specific susceptibility of mitosis has been provided in studies of rat corneal epithelium. Minimal daily doses of mustard when applied directly to the cornea can completely suppress mitosis during prolonged periods of treatment. The mitotic inhibition occurs in the absence of other evidence of epithelial damage, and after treatment is terminated the epithelium resumes its normal rate of proliferation. When the daily dose employed is raised tenfold, nuclear fragmentation becomes evident in a few scattered cells. A hundredfold increase in daily dose is required to produce sufficient cellular damage to cause permanent epithelial scarring. Inhibition of mitosis is, moreover, one of the manifestations of systemic injury noted in mammals treated with mustards. Small doses, sufficient to cause damage in hematopoietic organs and neoplastic tissues, elicit a prolonged period of atrophy in such tissues during which mitosis is significantly depressed.

Other mechanisms associated closely with the function of the cell nucleus have been shown to be susceptible to alteration by treatment with mustards. Thus structural changes have been observed in chromosomes of a variety of plant and animal cells following exposure to the agents. Such aberrations include chromosomal fragmentation, deletion and translocation. In addition to morphologic alteration, mustards readily induce genetic changes in chromosomes as evidenced by the fact that the agents have proved to be effectively mutagenic in various plant and animal species.

In view of the above cytologic and genetic disturbances of chromosomes it is impressive to note that other biologic entities containing large amounts of nucleic acid have also proved unusually susceptible to derangement by mustard treatment. Thus certain classes of viruses are readily inactivated by the agents *in vitro* when treated with concentrations that are effective in producing mitotic inhibition and chromosomal aberrations in growing cells. The capacity to reproduce intracellularly is most readily destroyed in those viruses which contain nucleic acids of the desoxyribose type. Furthermore pneumococcus-transforming factors, known to be composed almost exclusively of desoxyribose nucleic acid, also share the high susceptibility of the more sensitive viruses. These findings are to be considered in relation to current concepts of the importance of desoxyribose nucleic acids in the structure, function and reproduction of chromosomes and their component genes. The susceptibility *in vitro* of such "gene models" as viruses and transforming factors indicates that mustards might readily inactivate desoxyribose nucleic acids in cell nuclei. Presumably such interaction could disturb the reproductive capacity of intranuclear bodies and thereby cause suppression of mitosis, chromosomal aberration and gene mutation.

The suggested mechanism of nucleotoxic action is at best a plausible working hypothesis which derives indirect support from the fact that studies of a large variety of enzymatic systems both *in vitro* and *in vivo* have failed to implicate any of the known biologic catalysts as possible sites of the biochemical lesion caused by mustards. Although a number of enzymes have proved susceptible to inactivation by the agents, nevertheless the concentrations required

to inactivate the most sensitive catalytic proteins are several log orders greater than those necessary to induce nucleotoxic actions in proliferating cells or to inactivate viruses containing desoxyribose nucleic acids. However, there is at present a paucity of information concerning those enzymatic mechanisms which may be intimately and uniquely associated with the metabolism of the cell nucleus. Until such mechanisms are more fully explored and subjected to experimental treatment with mustards, it will be difficult to ignore the possibility that enzymatic systems could serve as primary sites of action of the mustards.

Additional qualifications must be attached to the acceptance of the aforementioned hypothesis. Although it offers some understanding of nucleotoxic activity, it fails to explain satisfactorily the extensive and rapid necrosis of proliferating cells which follows systemic intoxication in mammals. For example, the cell population of hematopoietic organs is drastically reduced to a scanty state within twenty-four hours after administration of minimum lethal doses of mustards. The cellular depletion is the result of an extensive, rapid necrosis and disintegration of lymphoid, myeloid and nucleated erythroid elements. It is conceivable that a relation could exist between such fulminating cellular derangements and interaction of mustards with vital loci in cell nuclei. Nevertheless there is no evidence to support such a contention.

DR. GELLHORN: We may say then that the nitrogen mustards, on the basis of the available evidence, strike at the nucleus and presumably alter nucleic acids or nucleoproteins. The nitrogen mustards are illustrative of the major problem in cancer chemotherapy because they show little selectivity, acting on normal as well as neoplastic cells. The most important factor which seems to govern the degree of action has to do with the rate of proliferation of the cells.

We will now turn to the folic acid analogues, drugs with which you are familiar at the clinical level. You will concede that these chemical compounds have striking biologic actions on tumor cells. This is most clearly demonstrated when a remission is induced in a child with acute leukemia. You have seen youngsters with high fever, with strikingly abnormal peripheral blood counts and bone marrow who, following administration of folic acid analogues, have a fall in temperature, conversion of the abnormal blood picture toward or to normal, and impressive subjective improvement. You are also familiar with the striking biologic action of folic acid analogues on normal cells. This is demonstrated by the effect on normal hematopoietic tissue and on the epithelial cells of the gastrointestinal tract. Again we are interested to inquire into the mechanism of action of these folic acid analogues. Dr. Jukes, who has been a pioneer in the study of folic acid, will give us information on this subject.

DR. THOMAS JUKES: The first evidence that folic acid plays a role in the formation of cells was obtained by Wills a number of years ago in early studies of nutritional macrocytic anemia in human subjects. These studies were concerned with folic acid deficiency as differentiated from vitamin B_{12} deficiency. Later, experiments on the nutrition of chicks by Professor Hogan of the University of Missouri demonstrated that on purified diets a macrocytic anemia was produced in young chicks which could be corrected by a substance present in yeast and liver. The role of folic acid in the metabolism of thymine was demonstrated about ten years ago by Snell and Mitchell who found that thymine could replace folic acid concentrates in promoting the growth of Streptococcus lacti. Also at about that time in studies with rats fed purified diets containing sulfonamides (sulfaguanidine in particular) it was found that agranulocytosis developed which could be corrected by feeding concentrates of the then unknown substance, folic acid, as prepared from liver and yeast. With these preliminary findings it was anticipated that when folic acid was isolated and synthesized, it might well be possible to prepare analogues which would block its cytopoietic action and would therefore produce changes marked by stopping mitosis in certain proliferating tissues. In 1947 some of these expectations began to be realized.

Folic acid may be synthesized by coupling dibrompropionaldehyde with p-amino benzoylglutamic acid and a triaminohydroxy-pyrimidine. By adding an extra methyl group to the dibrompropionaldehyde, that is, by using dibrombutylaldehyde instead, a substance or mixture was produced which was antagonistic to folic acid and which was reversed by feeding folic acid at higher levels. In studies with rats fed this folic acid analogue we described a syndrome which was characterized by agranulocytosis and anemia, diarrhea, necrotic and ulcerative changes in the mouth, loss of hair

and hypocellularity of the bone marrow. All these changes were reversed on raising the folic acid level of the diet by adding synthetic pteroylglutamic acid. When the amount of antagonist was increased, the signs reappeared; again they were abolished by increasing the level of the pteroylglutamic acid, showing a competitive inhibition between the metabolite and the antagonist.

The antagonist, so-called methyl folic acid, did not give encouraging results in the clinic in an attempt at treatment of leukemia, although it could be tolerated at a very high level. However, within a few months another compound was synthesized and in this case it was purified and characterized, namely, 4-amino folic acid or aminopterin. It had the unprecedented property of producing a pteroylglutamic acid deficiency, a folic acid deficiency, which was not reversible to any extent by feeding the metabolite, for reasons which we shall see later. Aminopterin is different from the folic acid molecule only by possessing an amino group in the 4 position instead of a hydroxyl group. Many studies were carried out with aminopterin. We should particularly like to mention the work of Dr. Philips with Dr. Thiersch at the Sloan-Kettering Institute, who made many careful studies of its profound and far-reaching effects in producing pathologic changes in various species of animals.

Aminopterin is characterized by being quite poisonous in low dosage (possibly more poisonous when it is fed mixed with the diet than when it is injected, although that is just a slight quantitative difference) and some results indicated that it would inhibit the growth of Rous sarcoma in chicks. Recently Bendich has found in rats that the administration of aminopterin reduces the amount of synthesis of adenine, guanine and thymine in the desoxypentose nucleic acid fraction and adenine and guanine in the pentose nucleic acid fraction.

Philips and Thiersch have noted its abortifacient effects in rats, and quite recently that report has been reinforced by an account of the effect of aminopterin in arresting progestational changes in rats and in rabbits which received progesterone. Aminopterin is evidently involved in mitosis, or rather the metabolites corresponding to aminopterin are involved in mitosis, as shown by metaphasic arrest which can be produced by adding aminopterin *in vitro* to certain cell preparations.

Dr. Gellhorn has already reminded us of the effect of aminopterin on acute leukemia in children. In a certain percentage of these children suffering from acute leukemias there is a temporary remission which lasts for periods varying from a few weeks to as long as two years but is nevertheless only temporary and is always followed with relapse. The changes in the mouths of the rats which received the folic acid antagonists are mirrored in the necrotic changes and swelling in the gums of patients who receive a few milligrams of aminopterin daily.

Similar changes were reported by Schoenbach recently. These changes can be reversed by the citrovorum factor. Aminopterin, although rightly considered a folic acid antagonist, is not readily reversible by pteroylglutamic acid. Sauberlich and Baumann reported the existence of a factor in liver extract and in certain other natural preparations, including yeast, which was needed by the lactic acid organism, Leuconostoc citrovorum. This growth factor had certain biologic properties in common with thymine and folic acid. Slow growth of the test organism could be produced by including very high levels of pteroylglutamic acid in the culture medium but the actual chemical nature of the compound remained unknown. Sauberlich also found that the citrovorum factor would reverse the inhibitory action of aminopterin on lactic acid organisms. Folic acid will reverse aminopterin for lactic acid organisms, although folic acid will not do it in animals. Sauberlich also noted that upon the administration of massive amounts of pteroylglutamic acid to human subjects the amount of citrovorum factor which was excreted in the urine was increased markedly.

We studied the relation of aminopterin, thymidine and the citrovorum factor in the nutrition of bacteria and mice. The response curve produced in L. citrovorum showed that the inhibitory effect of aminopterin was neutralized at three successive levels of citrovorum factor bearing a threefold relationship. Citrovorum factor was the true antiaminopterin substance, the competitive metabolite which reversed the action of aminopterin. With thymidine a noncompetitive antagonism was observed and this was also found with Escherichia coli. When Esch. coli was poisoned by high levels of aminopterin the poisoning was neutralized by adding thymidine. Thymidine appears to be the end product of the biochemical reaction, so

that when thymidine is furnished to L. citrovorum it no longer needs citrovorum factor and any interference with citrovorum factor is abrogated by the presence of the end product of the reaction.

When mice received injections of either 10 or 20 μg. of aminopterin every other day, after two injections 75 per cent of the mice were dead. They were not helped to any extent by being given comparable amounts of pteroylglutamic acid. When they received a concentrate of the citrovorum factor, which corresponded in biologic activity to 20 μg. of folic acid, the mice on the lower level of aminopterin all survived and maintained their weight. The mice on the higher level of aminopterin were protected partially but only three were left alive at the end of the ninth day, the assay period, again showing a competitive antagonism.

Burchenal and co-workers measured the response of leukemic mice to aminopterin. Without any addition the mice died in ten to fifteen days from leukemia. When aminopterin was administered, their survival time was increased to about thirty days; but when citrovorum factor and aminopterin were both given, leukemia reappeared. The antileukemic effect of aminopterin was neutralized by citrovorum factor. Folic acid was ineffective in reversing the effect of aminopterin in these mice. The mice getting both folic acid and aminopterin behaved like the mice getting aminopterin alone.

The biochemical implications of these findings are quite widespread. As was shown first for folic acid, there is also a connection between citrovorum factor and the formation of thymine and thymidine.

Another series of reactions with which folic acid is concerned is first the formation of formic acid from glycine and second, the formation of serine from formic acid and glycine. There is some indication that folic acid may be concerned with the oxidation of choline to form betaine but that is less clear-cut.

What is the reason for the extreme toxicity of aminopterin and for its antagonism towards the L. citrovorum factor? The synthetic citrovorum factor, leucovorin, has a formyl group attached to the 5 position on the pteridine ring. This pteridine ring has been partially reduced in forming leucovorin. In aminopterin there is an amino group in the 4 position. A good field for speculation is that another ring may form between the 4 and 5 positions when aminopterin is reduced *in vivo* to form a citrovorum factor-like compound, and that closure of this ring fixes the formyl group in such a way that it is unable to enter metabolic reactions.

DR. GELLHORN: We have seen, then, that in the case of the nitrogen mustards the mechanism of action is probably an alteration of the nucleoproteins in the nucleus. In the case of the folic acid analogues certainly an important mechanism of action is interference with the synthetic mechanisms which lead to the formation of nucleoproteins. It is on the basis of observations made with these two cytotoxic drugs and the fact that they do have some clinical efficacy that there has been keen interest in nucleic acids in the field of experimental cancer chemotherapy.

I should like now to discuss briefly a chemical compound which has been carefully studied in the laboratory because of its relationship to nucleic acid metabolism. This is 8-azaguanine, an analogue of guanine which Kidder at Amherst found to be effective in inhibiting the growth of experimental tumors. Kidder became interested in this compound through studies of the metabolism of an animal micro-organism, Tetrahymena geleii, which was unique in that it required guanine for its growth. When 8-azaguanine was added to the culture medium, the growth of tetrahymena was depressed. This finding prompted Kidder to search for other micro-organisms and viruses which might have a specific requirement for preformed guanine and which would therefore be susceptible to the action of the antimetabolite, 8-azaguanine. Although other microbes and viruses were not affected by the guanine analogue, an incidental screening test against several tumors in experimental animals revealed growth inhibitory activity. When this was reported two years ago, Drs. Engelman and Graff at this Institution were in the midst of a purine and pyrimidine analogue synthetic program and they made 8-azaguanine available to our laboratory. We confirmed and extended Kidder's observations on a broad spectrum of tumors and found that a variety of epithelial neoplasms were inhibited whereas leukemias and sarcomas were resistant to the drug's action. This dichotomy of effect on tumors suggested that the chemical compound might be an excellent tool to explore the biochemical differences between morphologically separable tumors.

Although studies of the mechanism of action of 8-azaguanine indicate that it alters nucleic

acid synthesis and may also modify the functions of nucleoprotein, I will not present the evidence because of lack of time. Rather, I will mention a series of observations which probably explain the reason for tumor sensitivity or tumor resistance to the drug. In our laboratory Drs. Kream, Hirschberg, Gertler and Gang have been studying the metabolism of 8-azaguanine. They have found that there is an intracellular deaminating enzyme which rapidly converts 8-azaguanine to 8-azaxanthine. This observation is interesting because 8-azaxanthine is completely inactive against tumor cells. The observation mentioned becomes quite significant, however, from a study of the distribution of the enzyme in a variety of normal and tumor cells. It has been found that the concentration of the deaminating enzyme is high in resistant tumor cells and low in the cells of those tumors which are effectively inhibited by 8-azaguanine. Thus a quantitative difference in a cellular component controls the amount of drug available for a chemotherapeutic action.

I have taken the time to present this story not because it tells of a development on the mainline of cancer chemotherapy research but rather because it illustrates the fact that quantitative variations in cellular biochemical patterns may be important in observing a chemotherapeutic effect. At the present time quantitative differences between normal and neoplastic cells are being carefully scrutinized for indications of possible vulnerable areas of attack on the malignant cell.

I should like now to summarize the discussion of two years of these clinics. First, it is to be stated again that at the present time there is no drug which can eradicate malignant disease. Second, at the present time it is apparent that the major problem in cancer chemotherapy is to find agents which will affect the neoplastic cell without affecting the normal cells, and the difficulties have been stressed in these clinics. Nevertheless it is to be emphasized that in spite of the fact that drugs such as the nitrogen mustards and the folic acid analogues do not do a completely adequate job in differentiating between normal and neoplastic cells, some differential does exist; we are able to get an effect on the neoplasm without destroying the host, and for this reason these agents at the present time do have a place in clinical therapy. It is, I think, important also to bear in mind that agents such as aminopterin and the nitrogen mustards do not affect all tumors. The folic acid analogues have an effect on leukemia. The nitrogen mustards affect the lymphomas. This indicates that there are subtle differences in the biochemical makeup of tumors of different origins. There is the further implication that cancer is not one disease but a multitude of diseases and moreover that it is extremely unlikely that one drug will be found which will have an effect on all cancers.

STUDENT: What are, at present, the general statistics on the clinical results of cancer chemotherapy?

DR. GELLHORN: In the main the available evidence indicates that the chemical compounds used in clinical cancer therapy fail to extend the duration of life significantly. This should not suggest that the drugs are of no practical value because in spite of their failure to prolong life they do provide symptomatic relief which permits the patient to lead a more useful and happy life than would otherwise be possible.

There are exceptions, of course, to the statement just made. Androgen control therapy of prostatic cancer does increase the duration of life; probably the life expectancy of children with acute leukemia is extended in those cases which respond to therapy and in selected patients with lymphomas, nitrogen mustard may be a life-saving treatment.

DR. HELEN RANNEY: Have any attempts been made to use combinations of some of the chemotherapeutic agents discussed today in the treatment of neoplastic disease? What have been the results?

DR. GELLHORN: That is an excellent question. Although the answer is no, the concept of combinations of chemotherapeutic agents has been explored in experimental cancer therapy using transplantable mouse tumors and it has been shown that the combinations are more effective than any one of the chemical compounds alone. It is entirely possible that the chemotherapeutic attack of the future will employ combinations which strike at several of the physiologic mechanisms of the cancer cell simultaneously.

The currently available cytotoxic agents do not lend themselves to being used in combination because their additive toxicity to the normal cells of the body would lead to catastrophe.

STUDENT: What are the criteria used in the selection of cancer patients for chemotherapy rather than surgery or radiation treatment?

DR. GELLHORN: There are two principal criteria. No patient should be considered for

chemotherapy to whom curative treatment by surgery or radiotherapy can be offered. Thus only patients with disseminated disease are candidates for chemotherapy. As has been mentioned in these clinics only a limited number of malignant tumors respond at all to the available therapeutic drugs so that the diagnosis is an important criterion also.

DR. RICHARD CROSS: There has been a lot of discussion on the relationship of certain viruses to cancer. Does this have any connection with nucleic acid metabolism?

DR. GELLHORN: One could write a book to answer this question—perhaps not a very good book, but certainly a big one! Suffice it to say that although there has been a great deal of discussion of the role of viruses as one of the possible initiating factors in the metabolic aberrations which lead to malignant change, this has not been conclusively demonstrated in either animal or human tumors. Since nucleic acid metabolism is important in virus and cancer biology there may well be some common connections; but what they are, if they exist, is not known.

DR. S. W. STANBURY: Is it true that all tumors that are sensitive to radiotherapy are also sensitive to nitrogen mustards?

DR. GELLHORN: No, this is not true. With the possible exception of bronchogenic carcinoma nitrogen mustard fails to modify the growth of other tumors of epithelial origin. As you know, radiotherapy is effective against a variety of epithelial tumors. There is no ready explanation for this difference in response of epitheliomas and lymphomas to nitrogen mustard except for the contribution which rate of cell proliferation may make in determining mustard susceptibility.

Although I have answered the question categorically, I should like to point out that the terms "radiosensitivity" and "radioresistance" are very poorly defined at the present time. We do not understand either the biologic or biochemical factors which determine these states and, in fact, the descriptions may be more apparent than real. Thus, as used clinically, a radiosensitive tumor is one which regresses or is eradicated with tissue doses of radiant energy which can be tolerated without irreversible damage by the surrounding normal tissues. A radioresistant tumor, on the other hand, may require as much or more radiotherapy than is compatible with the survival of surrounding normal cells. Even this description of the terms is inadequate for a radiosensitive tumor may practically be classified as radioresistant if the extent of the neoplasm is such that the cumulative dose to normal tissues, given incidental to the treatment of the tumor, is lethal to the host.

DR. WILLOUGHBY LATHEM: What is known about the mechanisms by which tumors develop resistance to nitrogen mustard?

DR. GELLHORN: It is not known whether tumors become resistant to the biologic action of nitrogen mustard. This phenomenon has not been clearly demonstrated in animals with experimental tumors.

Clinically we know that nitrogen mustard ultimately fails to provide significant therapeutic benefit in patients who initially had a good response. This, however, may well be due to the fact that the recovery of normal hemopoietic cells to the toxic actions of nitrogen mustard is slower than that of the tumor cells so that the disease progresses in the intervals between therapeutic courses. Eventually, then, treatment is indicated at a time when bone marrow depression resulting from chemotherapy and the underlying disease is sufficiently great that further mustard would cause lethal complications. At this point we may say that the tumor has become mustard-resistant whereas more accurately we should note that the toxicity to the host prohibits further therapy.

In the case of aminopterin it can be demonstrated experimentally that the drug acts as a selecting agent which by destroying susceptible leukemic cells permits the undiluted growth of a population of mutant cells completely resistant to the action of the drug. As in the case of studies with the antibiotics, experiments have been reported in which successive generations of leukemic cells exposed to aminopterin treatment have not only led to the development of aminopterin resistant strains but also aminopterin dependent strains.

SUMMARY

DR. GILBERT H. MUDGE: The chemotherapy of malignant disease has been discussed with particular emphasis on the biology of cancer and the mechanisms of action of various chemotherapeutic agents. The metabolism of nucleic acids has been stressed because of their undoubtedly important role in the biologic reactions under consideration.

Nucleic acids are found in all living cells and may be divided into two main groups. The desoxypentose nucleic acids occur mainly within nuclei while the pentose nucleic acids are found chiefly within the cytoplasm. Their physical and chemical properties are briefly reviewed. Present evidence strongly indicates that nucleic acids represent the chemical basis of chromosomes and as such play a central role in the mitotic activity of both normal and malignant cells.

The nitrogen mustards are unquestionably of great use in the treatment of certain types of malignancy. Their pharmacologic action is reviewed in relationship to chemical structure. These compounds react rapidly with a variety of chemical groupings. A careful analysis of minimally effective concentrations reveals mitotic activity to be the cell function most sensitive to their action. The evidence is reviewed which suggests a specific effect upon nucleoproteins.

The analogues of folic acid represent another group of agents employed in the treatment of malignancy. Their use has permitted precise definition of the role of folic acid in hematopoiesis as well as in nucleic acid metabolism. Studies with aminopterin have revealed that it blocks intermediary reactions leading to the synthesis of nuclear proteins and that the metabolic block is competitive in type. The probable site of this block is discussed in relationship to the action of the citrovorum factor.

A different aspect of cancer chemotherapy is discussed in relationship to the action of 8-azaguanine. This antimetabolite has a marked effect upon certain tumors but no effect upon others. In this instance it has been possible to demonstrate that the specificity of the drug action can be correlated with the metabolism of the tumor. Thus normal tissue and resistant tumors can inactivate the drug while sensitive tumors contain low concentrations of the inactivating enzyme.

It is emphasized that the successful development and employment of chemotherapeutic agents for the treatment of cancer will depend upon further knowledge of the specific metabolic abnormalities of the malignant cell. The subtle differences in the biochemical makeup of different tumors makes it extremely improbable that any single drug will ever become a panacea for all cancers.

Clinico-pathologic Conference

Calcific Aortic Stenosis and Convulsions

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. C. (No. 184135), a white, retired painter and cabinet maker sixty-nine years of age, entered the Barnes Hospital for the first time on May 2, 1950, because of a cough productive of yellow, blood-tinged sputum. The family history was of interest only in that one brother had been bed-ridden for several years with "miner's consumption." The past history revealed that the patient had been in essentially good health until eight years prior to admission when he was told that his blood pressure was elevated. Although he began to have episodes of palpation at this time he had no other symptoms suggestive of cardiac decompensation or of other cardiac disease. Three years before entry he developed malaise and a cough productive of yellow, blood-tinged sputum. These symptoms persisted for six weeks and then disappeared, and the patient was apparently well until six months before admission when he again began to cough. Once again he produced yellowish sputum which contained bright blood. He lost weight rapidly and consulted a physician who took a chest x-ray and told the patient that he had a "shadow" in the left lung. He was referred to the State Cancer Hospital where further x-ray studies were made and bronchoscopy was done. The patient was informed that the lesion in the left lung was not due to cancer or to tuberculosis. While in the hospital, however, he was found to have glycosuria and was regulated on a suitable diet. Because his pulmonary symptoms persisted after discharge from the Cancer Hospital, he entered the Barnes Hospital for further study. He had not smoked for seven years prior to entry.

Physical examination at the time of entry revealed the temperature to be 37.2°C., pulse 72, respirations 20 and blood pressure 150/90. The patient appeared chronically ill and emaciated, and he coughed continually. Fine rales were heard over the left scapular area. Examination of the heart revealed high pitched, blowing systolic murmurs at the apex and at the aortic area. There was 1+ bilateral pitting edema of both legs. The remainder of the physical examination was within normal limits.

The laboratory findings included a moderate normocytic, normochromic anemia. The white blood cell count was 12,950, and the differential count showed 15 stab forms and 72 segmented forms. The fasting blood sugar was 305 mg. per cent. Roentgenograms of the chest revealed infiltration in the apical portion of the left lower lobe. Calcification of the aortic ring was also demonstrated. An electrocardiogram showed left ventricular enlargement, ventricular premature contractions and a prolonged P-R interval (0.24–0.26 seconds).

Shortly after admission the patient was subjected to bronchoscopy; 5 per cent cocaine was used as the local anesthetic. The left main bronchus was visualized and considerable reddening and edema of the mucosa was noted. Further examination was interrupted because the patient developed a minor convulsive seizure. His pulse became irregular and weak, and then was unobtainable for a short period of time. His respirations decreased to ten per minute and he became unresponsive. Oxygen therapy was immediately instituted and the patient made a prompt recovery. The episode was considered to have represented a reaction to cocaine. During the patient's hospital stay many sputum examinations were negative for acid-fast organisms. Several examinations of the sputum for cancer cells were likewise negative. The venous pressure and circulation time were normal.

On a regimen which included bed rest, intensive parenteral and aerosol penicillin therapy and an adequate diet, the patient improved markedly. Sputum production was much decreased, and the infiltrative lesion in the lung

decreased strikingly. The patient's diabetes was suitably controlled and he was discharged with a diagnosis of lung abscess. He was advised to continue aerosol penicillin.

The patient's second and last admission to the Barnes Hospital on July 6, 1951, was occasioned by repeated convulsions. On this admission additional historical data obtained indicated that eight years previously the patient had fallen down a flight of stairs striking his head against a cement wall. He did not lose consciousness, was apparently not injured, and attached no significance to the episode, although six months later he had the first of a series of convulsive seizures which were preceded over a three- to four-day period by a generalized severe headache. The first seizure occurred while the patient was asleep. His wife reported that he was at first rigid, then had generalized convulsive movements and chewed his tongue. During the attack his hands were said to have become "black." The seizure lasted about thirty minutes, but the patient was then unable to communicate with his wife for another hour. The next day he complained of back ache and sore muscles. Ten months before admission his right arm became swollen and black. He was advised to undergo amputation but refused, and the arm gradually returned to normal. Similar convulsive seizures occurred every few months until one year before entry at which time they became more frequent. In the three weeks prior to admission they had occurred daily. The most recent attacks were preceded by a sensation of "a veil pulled down" in front of his face. At no time was focal weakness noted, but the patient apparently had had a gradual loss of memory over the last year. He consulted a physician who prescribed phenobarbital tablets, but these did not control his seizures and he was referred to the Barnes Hospital for further study.

Physical examination revealed the patient's temperature to be 37.5°C., pulse 78, respirations 16 and blood pressure 140/84. He was quite emaciated but did not appear acutely ill. Ophthalmoscopic examination revealed moderate sclerosis of the retinal vessels, but no hemorrhages, exudates or papilledema were seen. The upper respiratory tract appeared normal. The trachea was in the midline and the neck veins were not distended. The lungs were clear to percussion and auscultation. The cardiac impulse was palpated 7.5 cm. to the left of the midline in the fifth interspace. The heart sounds were distant and the rhythm was regular. A grade III systolic musical murmur was heard over the aortic area and was transmitted up the neck vessels. A similar murmur was heard in the mitral area and was transmitted over the lateral aspect of the precordium. No thrill could be felt. The peripheral vessels were sclerotic. The liver edge extended 2 cm. below the right costal margin and was soft and non-tender. Rectal examination was negative. The extremities were normal. The only abnormalities in the neurologic examination were slight generalized weakness of all muscle groups, equal, depressed deep tendon reflexes, and a positive Romberg test, the patient tending to fall to the left or backward.

The laboratory data were as follows: Blood count: red cells, 3,710,000; hemoglobin, 13 gm. per cent; white cells, 14,250; differential count: eosinophils 6 per cent, stab forms 5 per cent, segmented forms 68 per cent, lymphocytes 20 per cent, monocytes 1 per cent. Urinalysis: specific gravity 1.018; albumin 1+; sugar 3+; sediment, negative. Stool guaiac: negative. Blood cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 34 mg. per cent; sugar, 230 mg per cent; calcium, 12.4 mg. per cent; phosphorus, 5.7 mg. per cent; total protein, 6.1 gm. per cent; albumin, 3.7 gm. per cent; globulin, 2.4 gm. per cent; sodium, 150 mEq./L.; potassium, 5.1 mEq./L.; chloride, 108 mEq./L. Roentgenogram of the chest: since the previous examination there was a marked increase in the pulmonary vascular markings throughout both lung fields, more marked in the hilar region; the pulmonary arteries appeared extremely large. Cardiac enlargement was of greater degree than noted previously, and was left ventricular in type. Calcification of the base of the aorta was again noted. Roentgenograms of the skull: negative. Electrocardiogram: left ventricular enlargement; left ventricular strain, prolongation of the P-R interval (0.24 seconds). Electroencephalogram: mild, irregular slow dysrhythmia, not significantly altered in view of the patient's age.

Shortly after admission the patient had a brief convulsion characterized by tonic contraction of the muscles, followed by short clonic movements and transitory loss of consciousness. He was given dilantin, 0.1 gm. three times daily, and phenobarbital, 30 mg. three times daily, but continued to have frequent seizures. The phenobarbital dosage was increased to 65 mg. in the morning and 90 mg. in the evening, and no further

seizures occurred. A lumbar puncture revealed normal dynamics; the cell count and protein were normal, and the colloidal gold curve and Wassermann reactions were negative. The patient's diabetes was regulated by means of diet and 20 units of NP insulin each morning. The blood sugar remained elevated above 200 mg. per cent, but the urinary sugar decreased to a trace. Toward the end of the first hospital week the patient's pulse rate became 44 per minute, and an electrocardiogram revealed 2:1 auriculoventricular block. Increasing T wave inversion was noted in most of the leads. The bradycardia was little affected by atropine in doses of 0.4 mg. daily.

Toward the end of the second week the patient became short of breath. The venous pressure was found to be 200 mm. of water, the circulation time (decholin) was 23 seconds, and rales were heard at the lung bases. His temperature, which had been within normal limits, rose to 38.2°C. and the white blood cell count was 10,400. The patient was digitalized and penicillin and streptomycin therapy was instituted. The temperature continued to rise, reaching 39.4°C.

On August, 7, 1951, the twelfth hospital day, an electrocardiogram revealed complete auricular-ventricular dissociation with an auricular rate of 120 and a ventricular rate of 45. On the following day while he was being examined the patient suddenly expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: There were three major facets to this patient's history as recorded in the protocol. On his first admission to the Barnes Hospital, which was occasioned by symptoms and signs of pulmonary disease, he was found to have a cardiovascular lesion also. His second and last admission was because of repeated convulsions. Whether the lesions involving the lungs, heart and central nervous system were related or not will have to be determined. It may be well to consider first the nature of the pulmonary disease; since the patient apparently recovered completely from this illness, it may not have been significant in the over-all picture. He entered the hospital with a history of productive cough of six months' duration, and during his stay many studies were carried out in an attempt to determine the nature of the infiltrative lesion in the left upper lobe. Numerous sputa were negative for acid-fast organisms and for carcinoma cells. The patient improved remarkably on antibiotic therapy and he was discharged with a presumptive diagnosis of lung abscess. Dr. Goldman, is lung abscess as common now as it formerly was?

DR. ALFRED GOLDMAN: No, I think it occurs much less frequently.

DR. ALEXANDER: Would you tell us why?

DR. GOLDMAN: There are two factors responsible, at least to a considerable extent, for the decrease in the incidence of lung abscess. First, many cases of lung abscess formerly occurred following tonsillectomy and other operative procedures on the month and upper respiratory tract. Greater awareness of the danger of aspiration and improvement in the technics of anesthesia employed in such procedures has resulted in a marked decrease in cases of this type. Second, and probably much more important, has been the introduction of chemotherapeutic agents which have made it possible to treat bacterial pneumonia much more effectively than previously. Respiratory infection can be controlled now so much more satisfactorily than was ever possible prior to the advent of antibiotics, that the decrease in lung abscess can, I feel sure, he explained to a large extent on this basis alone.

DR. ALEXANDER: Dr. Wood, this patient was given aerosol penicillin. Would you comment on the use of the aerosol route as a means of giving antibiotic therapy?

DR. W. BARRY WOOD, JR.: I think that aerosol therapy should not be relied upon alone. As was done in this instance, the parenteral route should be employed; and if it seems advisable, aerosol penicillin may be given as a supplementary measure. The situation which obtains in pulmonary infection is somewhat analogous to that in bacterial meningitis in which parenteral chemotherapy is always given, frequently with intrathecal therapy as an adjunct.

DR. ALEXANDER: Isn't it true that penicillin given as an aerosol may in some instances never reach the lesion?

DR. WOOD: That is an important point. If the nebulized particles are not of the correct size, they will never penetrate into the lung parenchyma. Suitable bronchodilators should probably be given concurrently when the aerosol route is used.

DR. GOLDMAN: My experience with aerosol therapy has not been particularly encouraging,

but favorable results have been reported by some observers. The point that has been made in regard to the size of the nebulized particles is an important one.

DR. ALEXANDER: Let us now proceed to a discussion of the interesting cardiac findings. Dr. Wilson, would you comment on the films in regard to the cardiovascular abnormality?

DR. HUGH M. WILSON: Considerable calcification in the area of the aortic ring was noted repeatedly in the patient's films and when he was fluoroscoped. (Figure 1.) It is difficult to be sure how much of the calcium lay in the valve and how much in the base of the aorta. The valve was almost certainly involved. At the time of his second admission there was a moderate increase in heart size and the cardiac contour suggested left ventricular enlargement.

DR. ALEXANDER: Certainly the roentgenologic findings plus the presence of a grade III systolic murmur over the aortic area, transmitted up the neck vessels, were consistent with the diagnosis of calcific aortic stenosis. On several occasions varying degrees of heart block were also recorded. Dr. Massie, may the latter finding have been related to calcific aortic stenosis?

DR. EDWARD MASSIE: Auriculo-ventricular block is noted frequently in aortic stenosis and may reasonably be considered a common feature of that lesion.

DR. ALEXANDER: When A-V block does occur in aortic stenosis, what is the reason for it?

DR. MASSIE: It has been postulated that calcification may be extensive enough to involve the bundle of His in the fibrous septum, thus giving rise to A-V block. How often this happens in fact is not known. It has also been suggested that myocardial ischemia, due to functional coronary insufficiency, may explain conduction defects.

DR. ALEXANDER: We saw a patient recently with calcific aortic stenosis who succumbed to the disease. At postmortem examination extension of calcium into the fibrous septum was demonstrated. Dr. Moore, is it difficult for the pathologist to show involvement of the conduction system by calcium in this disease?

Dr. ROBERT A. MOORE: It can be done on occasion if a tremendous number of serial sections is made.

DR. ALEXANDER: As I said previously, it seems clear that this patient had calcific aortic stenosis. Dr. Smith, do you think there was also a mitral lesion?

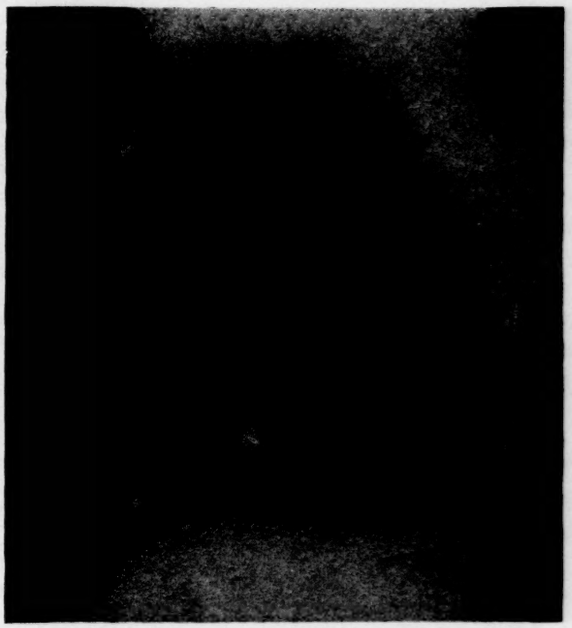


FIG. 1. Roentgenogram of the thorax showing an annular shadow of calcification at the base of the heart.

DR. JOHN R. SMITH: The harsh systolic murmur described at the mitral area may well have been due to calcific deposits in the mitral valve leaflets. One cannot rule out the possibility that the murmur heard at the mitral area was transmitted from the base of the heart.

DR. ALEXANDER: Dr. Massie, do you believe this patient had coronary artery disease?

DR. MASSIE: The electrocardiograms showed primarily only left ventricular enlargement.

DR. ALEXANDER: Is coronary artery involvement common in calcific aortic stenosis?

DR. MASSIE: There is not necessarily a positive correlation between calcific aortic stenosis and coronary artery sclerosis. In this particular case it must be remembered that the patient was sixty-nine years of age, and was thus entitled to some coronary artery disease on the basis of his age alone. As I have indicated, however, the electrocardiogram gave no evidence of significant myocardial damage, and there was nothing in the history to suggest it to me.

DR. ALEXANDER: Are there any further comments in regard to the patient's cardiovascular disease?

DR. WOOD: In the consideration of the etiology of calcific aortic stenosis it is of interest to point out that rheumatic fever or arteriosclerosis *per se* are not the only causes to be considered. There seems to be some evidence that healed

bacterial endocarditis may be responsible for calcific aortic stenosis in some instances.

DR. ALEXANDER: Would you comment, Dr. Hunter, on the relation of healed bacterial endocarditis to calcific aortic stenosis?

DR. THOMAS H. HUNTER: There can be no question that the histologic findings in certain stages of healing bacterial endocarditis are extraordinarily similar to those noted in calcific aortic stenosis. It seems to me quite reasonable to assume that some cases of calcific aortic stenosis arise on that basis. I cannot, however, believe that healed bacterial endocarditis accounts for all cases of calcific aortic stenosis, because I do not believe the diagnosis of bacterial endocarditis is missed that often. Certainly one finds the signs of calcific aortic stenosis in patients who give absolutely no history suggestive of bacterial endocarditis.

DR. ALEXANDER: Let us take up now the problem of recurrent convulsions which led to the patient's second admission. Dr. O'Leary, would you discuss the present concept of the pathogenesis of convulsions.

DR. JAMES L. O'LEARY: At the outset it will be assumed that the normal brain, synchronizing the discharges that are associated with purposeful activity at any level of the neuraxis, is provided with a mechanism not only for the excitation of discharge but also for the restraint of discharge. This assumption was put forth originally by Gowers. In seizure phenomena the restraint mechanisms, for one or another reason, apparently become relatively inoperative, and the normally synchronized electrical phenomena of the nervous system become excessively synchronized and "spray" as it were in avalanche fashion over the forebrain structures and the diencephalon to the lower levels of the nervous system. The overt manifestations of such a discharge are the tonic and clonic movements of a convulsion. If one records brain activity during a typical grand mal seizure, one finds very high voltage, spike-like discharges which are rapidly repetitive. These discharges have 40 to 50 times the voltage of the normal electrical activity of the brain and persist until the seizure is over. The fact that such a pattern occupies all available circuits during the seizure means that there is loss of consciousness for there are no neurons participating in normal activity; all are involved in the seizure discharge. One would expect, therefore, that such seizures would occur under most circumstances when there was a high level of excitability of the nervous system so that they could be rapidly triggered. Such is probably the case frequently in so-called idiopathic epilepsy. It should be noted, however, that marked convulsive phenomena may occur in a relatively morbid brain. Thus any disease state which interferes with oxidative glycolysis over a period of time as, for example, hypoglycemia due to insulin shock, or cerebral anoxia secondary to cerebral arteriosclerosis, may cause convulsions. These comments have been oversimplified, but they represent generally our current concepts.

DR. ALEXANDER: Dr. Levy, would you continue the discussion?

DR. LEVY: From this point on it becomes a matter of application of theory to clinical material. In the particular patient whom we are discussing today so many factors are involved that it is difficult to incriminate any one. First of all, the question of the role of trauma arises. This patient sustained a head injury eight years before admission. He did not lose consciousness, and apparently considered it of little significance at the time. Six months later, however, he began to have seizures. It should be pointed out here that head trauma of a presumed minor nature may give rise subsequently to convulsive seizures. Thus as a result of trauma to the head perivascular lesions may occur with resulting loss of neurons, which in turn affords the basis for a convulsive mechanism. Focal trauma with scarring may also lead to convulsions. Another factor to be considered in this patient is the possibility of arteriosclerosis. With advancing age a certain percentage of patients develop convulsions because of arteriosclerosis *per se*, even though they have never had convulsive disorders of any type previously. Whether such convulsions are due to small areas of brain softening or merely to anoxia is difficult to determine; there may be no focal lesion in such cases. This patient also had heart block. Convulsions may occur in association with heart block as, for example, in the Stokes-Adams syndrome. The problem of diabetes and its relation to convulsions must be considered. In diabetes the associated arteriosclerosis may cause convulsions as I have already indicated. Terminally, this patient developed cardiac decompensation which may have led to increased anoxia and altered irritability of the nerve cells.

DR. ALEXANDER: Would you comment, Dr. Levy, on the probable etiology of convulsions in different age groups?

DR. LEVY: As a general rule seizures in different age groups are due to different conditions. Childhood convulsions may be associated with disturbances in calcium metabolism, as a result of brain injury at or after birth or because of defective development. In patients with a family history of idiopathic epilepsy seizures often begin in early life. In this regard it should be noted that after the age of 25, there is a sharp decrease in the incidence of *initial* convulsive episodes arising on the basis of hereditary disease. An additional prominent etiologic factor for convulsions in childhood, is high fever, usually associated with infectious disease. In young adults initial seizures suggest most commonly brain tumors. In middle life tumors and hypertension are perhaps the most common causes. In elderly patients, as I have already indicated, there are many possibilities, and in some patients in this age group, no definite cause can be demonstrated.

DR. ALEXANDER: Dr. Erlanger, do you believe that this patient's convulsions arose on the basis of Stokes-Adam's syndrome?

DR. HERMAN ERLANGER: Yes, I think that they probably did.

DR. MASSIE: I would agree with Dr. Erlanger.

DR. ALEXANDER: The patient's wife stated that his convulsions lasted for about a half an hour. Certainly patients with Stokes-Adams attacks may be unconscious for rather long periods of time, but how long do the convulsions associated with Stokes-Adams attacks usually continue?

DR. O'LEARY: I think that the convulsions associated with Stokes-Adams syndrome are usually short-lived. There may be recurrent seizures, however, so that observers may get the impression of a single prolonged convulsion.

DR. ALEXANDER: Dr. O'Leary, this patient had an encephalogram which was apparently within normal limits for his age group. That information does not help in the differential diagnosis, does it?

DR. O'LEARY: No.

DR. ALEXANDER: May we consider briefly now the cause of this patient's sudden death. Dr. Wood, do you have any suggestions in this regard?

DR. WOOD: Sudden death is not uncommon in aortic stenosis. It is said that occasionally the valves "lock." Any patient with heart block may die in asystole. Commonly no explanation of death is found and I expect that none will be apparent in this case.

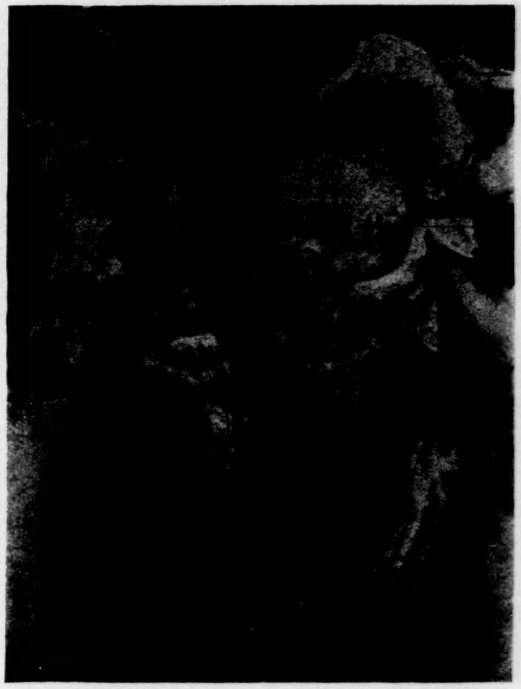


FIG. 2. The aortic valve with a perpendicular incision exposing the edges of a cusp and a sinus of Valsalva. Note the ring of calcified nodules about the base of the aorta at the level of the commissures and also at the level of the bases of the cusps, and that the cusps themselves are only slightly thickened.

DR. ALEXANDER: In summary, this patient apparently suffered from a pulmonary lesion, probably a lung abscess, from which he recovered without significant residual. He had calcific aortic stenosis and possibly calcific mitral disease as well. The convulsive disorder which led to his final hospital admission could have been due to the trauma which he suffered eight years before entry, but it also may have been associated with arteriosclerosis *per se*, or with heart block.

Clinical Diagnoses: Generalized arteriosclerosis; calcific aortic stenosis.

PATHOLOGIC DISCUSSION

DR. RICHARD L. SWARM: The heart was enlarged and weighed 600 gm. A number of intimal plaques narrowed the lumens of the coronary arteries, but at no point was there complete obstruction. The leaflets of the mitral valve were thickened at their bases and the

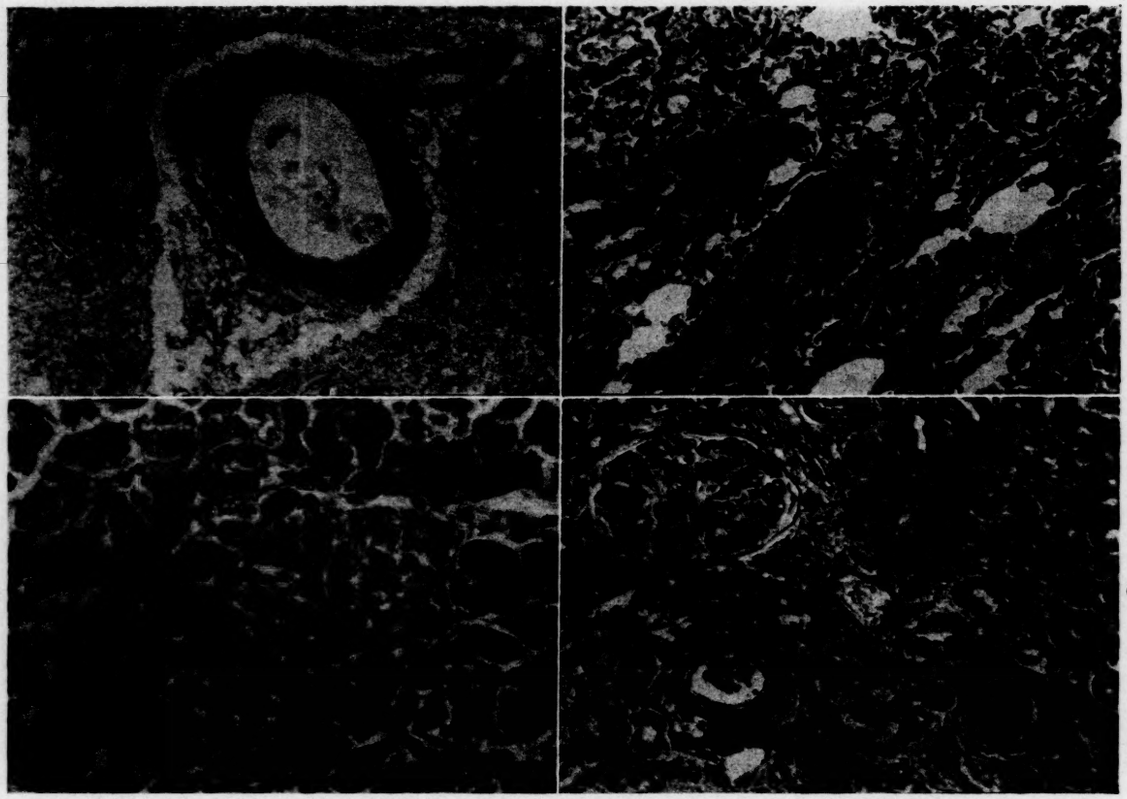


FIG. 3. Calcification of the media of a small artery in the globus pallidus. This calcification of the small cerebral arteries was very striking but cannot be specifically related as either cause or effect of the epilepsy.

FIG. 4. A section of lung showing only atelectasis and slight congestion and edema, but no evidence of the chronic inflammatory process expected from the history.

FIG. 5. Hyalinization of an islet of Langerhans, a lesion that can be correlated with diabetes mellitus.

FIG. 6. Arteriolar nephrosclerosis with prominent sclerosis of small arteries in the kidney.

mitral ring was completely calcified. A ring of calcified nodules surrounded the base of the aorta just above the valve cusps (Fig. 2) and the aortic ring itself was calcified. The aortic valve cusps were thickened and firm and more calcified nodules were present at their bases deep in the sinuses of Valsalva. The commissures showed only slight adhesions. The circumference of the aortic valve at autopsy was 66 mm. which is about 10 mm. less than usual for a heart of this size. The lungs showed scattered fibrous pleural adhesions but no focal lesions in the parenchyma except for a calcified nodule and bilateral thickening of the apical pleura. There were 300 cc. of clear fluid in the right pleural cavity and 250 cc. in the left. The liver and spleen were moderately congested. Each kidney had the granular surface and reduced cortical thickness of moderate arteriolar nephrosclerosis. Otherwise the viscera contained no relevant lesions. The brain was remarkable only for a slight symmetrical dilatation of the lateral ventricles, scattered fibrous thickening of the leptomeninges and arteriosclerosis of the cerebral arteries.

DR. ROBERT A. MOORE: We might first consider this extremely interesting aortic valve and ring. Calcific aortic stenosis was described in the last century as a lesion consisting of calcification of the aortic valve and the aortic ring, associated with arteriosclerosis. During the last twenty years there has been increasing dissent from that interpretation of the pathogenesis; some authorities now believe that endocarditis is the cause while others reject either as the explanation of all instances of this lesion. In the illustration it can be seen that in this case the great mass of the calcium was in the wall of the aorta above the aortic valve; it was not in the leaflets of the valve. There was calcification in the base of the valve and at the bottom

of the sinus of Valsalva. It is to be noted that the latter calcification did not involve the ventricular surface or project toward the lumen of the heart as is characteristically seen in the usual lesion of calcific aortic stenosis. If there are two types of calcific aortic stenosis, this seems the less likely to be due to endocarditis because the calcification was primarily in the ring and the aortic wall and not in the valve. It is also important in this case that these calcified masses did not project far into the lumen of the aorta or render the valve leaflets rigid and were actually small in comparison with those in most cases of calcific aortic stenosis.

For the remainder of the cardiovascular system it was apparent that the patient had advanced arteriosclerosis of the coronary arteries, cerebral arteries, aorta and other vessels. There was vascular disease of the kidney of moderate degree and the heart was considerably hypertrophied. The brain showed a slight to moderate degree of internal hydrocephalus. Sections gave some evidence of a loss of nerve cells throughout the cortex and basal ganglia, and Figure 3 illustrates the rather striking calcification of the media of the small arteries that was present in the globus pallidus and thalamus. This lesion is often discovered incidentally and is at most evidence only of vascular disease. From the anatomic examination of the brain the severity of the effects of this vascular disease was indicated by the internal hydrocephalus and the loss of nerve cells. This evidence of a diffuse degeneration was the apparent explanation of the disease of the central nervous system in this patient as no focal lesions of traumatic or other origin that might have been related to the epilepsy were found.

In the lungs we were unable to find anything which represented a residual of the lesion interpreted clinically as a lung abscess. It seems likely, therefore, that lesion was more of the nature of an infarct which is known to heal as an imperceptible flat scar. The bronchial mucosa was red and slightly thickened, but no more advanced lesion that could be correlated with the clinical history of pulmonary symptoms was apparent. A section of the lung (Fig. 4) showed only atelectasis, congestion and edema.

In Figure 5 there is illustrated a very good example of hyalinization of the islets of Langerhans. This lesion is found in a significant percentage of persons who have diabetes; and when it is as advanced and well developed as this with only a few cells left in homogenous, lobular eosinophilic hyalin, it is practically pathognomonic. In this case there were no lesions in any other parts of the body that gave evidence of diabetes. The kidney (Fig. 6), for instance, showed only the rather marked arteriosclerosis in the small arteries and arterioles of arteriolar nephrosclerosis.

The anatomic findings provide no clear explanation for many of the cardiac symptoms discussed clinically. There are two possibilities that may have been of importance in the heart block. First, the calcified nodules at the base of the aortic valve may have impinged upon the conduction bundle, and second, the severe coronary arteriosclerosis which is known to result in heart block by causing fibrosis of the myocardium in the region of the bundle of His may have been responsible for the arrythmia. Passive congestion of the lungs, liver and spleen indicated a distinct degree of cardiac failure, but there is no patent anatomic explanation for this man's sudden death. The one disease process of arteriosclerosis seems to have been behind the cerebral changes and the epilepsy, the pancreatic changes and the diabetes, and the vascular changes and the heart disease; thus arteriosclerosis can be said to have been basically responsible for the diverse symptomatology in this case.

Final Anatomic Diagnoses: Advanced arteriosclerosis of the coronary and cerebral arteries and the aorta; calcification of the rings of the aortic and mitral valves and of the base of the aorta; arteriolar nephrosclerosis; atrophy of the cerebral cortex; hyalinization of the islets of Langerhans.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Report

Chickenpox with Visceral Involvement*

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New York, New York

CHICKENPOX has been known for many years, dating from the first quarter of the nineteenth century when it was distinguished from smallpox. It has usually been considered to be a mild, self-limited disease affecting principally young children. Only in recent years has it been recognized that adults may acquire the infection; that there may be widespread and fatal visceral involvement is still not generally known.

In textbooks chickenpox is stated to have few complications. These are usually pyogenic infections, most often of streptococcal or staphylococcal etiology. However, in rare instances visceral manifestations have been attributed to direct viral involvement of the respective tissues.

There are few reports of autopsies on patients with chickenpox. Probably the earliest description of specific pathologic changes in the internal organs was that of Schleussing[1] in 1927. He reported the postmortem findings on twins who had been born prematurely and were three weeks old at the time of their death from chickenpox. In addition to changes in the skin the principal findings were areas of focal necrosis in the liver, spleen and adrenals. Waring et al.[2] reported the case of an adult who died with pneumonia and encephalitis complicating chickenpox. The noteworthy pathologic findings were focal pneumonia of mononuclear type with proliferation of alveolar septal cells and necrosis, perivascular cuffing in the brain and renal tubular degeneration. The occurrence of inclusion bodies was not mentioned in either of these reports, and no other evidence was presented to indicate that the lesions were specific for the disease or caused by a virus.

Up to the present time the only acceptable and readily obtainable evidence of infection of a tissue by the virus of chickenpox is the demonstration of characteristic intranuclear inclusion bodies. Recovery and identification of the virus by injection into experimental animals is rarely if ever successful. Most observers[3] are of the opinion that the virus has not been transferred to experimental animals nor grown on the chorio-allantoic membrane of chick embryos. Recently Weller and Stoddard,[4] employing a human embryonic tissue culture system, observed the development of eosinophilic intranuclear inclusion bodies in tissue cells following inoculation with varicella vesicle fluid. Attempts at serial passage in subcultures were unsuccessful. "Elementary bodies" have been demonstrated in the vesicle fluid of early skin lesions of chickenpox by use of electron microscopy.[5] A rising serum complement fixing antibody titer using antigen from varicella crusts or vesicle fluid[3b] has been reported to be of value in confirming the presence of chickenpox infection but is of no assistance in demonstrating involvement of any specific tissue.

The intranuclear inclusion bodies in chickenpox infection were first described by Tyzzer.[6] He emphasized the constancy of their occurrence but did not account for their appearance or ascribe any functional significance to them.

Inclusion bodies were known to occur in many other viral infections but it was not until 1926 that Kuttner and Cole[7] first demonstrated the viral causation of one type of intranuclear inclusion. Cowdry[8] greatly elaborated on the description of intranuclear inclusions and classified them as Types A and B. The inclusions found in infections due to the viruses of chickenpox and herpes zoster, as well as in several other viral diseases, he classified as Type A. In this category the entire nucleus is involved, with an accumulation of acidophilic material in the center, surrounded by a clear zone and then a thin rim of basophilic material at the periphery. Ultimately there is complete disintegration of the entire nucleus and then of the entire cell, and a marked tissue reaction with infiltration of phagocytic cells.

In a recent review[9] Pinkerton re-emphasized

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the importance and the diagnostic value of the recognition of viral inclusion bodies. He also pointed out some of the erroneous interpretations to be avoided.

The first reported observation of intranuclear inclusions in the internal organs of a patient with chickenpox was made by Johnson[10] in 1940. This was in the case of a seven month old boy who showed focal degeneration of the esophagus, liver, pancreas, renal pelves, bladder and adrenals, with intranuclear inclusions in most of these tissues as well as in the skin.

Since that time similar reports[11] have appeared with increasing frequency. To date, five cases have been reported including two newborn infants, one baby and two adults. Although almost every organ or tissue has been involved in one case or another, epithelial cells predominantly have shown the intranuclear inclusions. Only in Johnson's case[10] were inclusion bodies found in vascular endothelium. These were also observed in the present instance.

This case is being reported because the opportunity to observe visceral chickenpox is uncommon and its existence is not generally recognized. Among the noteworthy features were the age of the patient and the presence of inclusion bodies in cells of granulation tissue in an incidental sarcoidosis.

CASE REPORT

The patient was a seventy-one year old white woman who was admitted to The Grace-New Haven Community Hospital on February 14, 1951, with the chief complaint of generalized dermatitis. Her past history was entirely negative. She had had no major illnesses or operations and she did not recall having had any childhood disease except measles. The present illness began ten days before admission when the patient noticed a small nodule in the skin over the left eyebrow. She did not recall an insect bite or trauma in this area, and there was no known exposure to any infectious disease, including chickenpox. During the next three to four days successive crops of lesions appeared on the skin over the entire body, starting as papules and progressing to vesicles with crusting. A diagnosis of chickenpox was made by her physician. She was treated with terramycin, 500 mg. every six hours, for the five days prior to admission, with no response.

The rash was non-pruritic and was associated with no other symptoms, except for moderate anorexia, and with nausea and vomiting while receiving the antibiotic. The patient remained afebrile and felt quite well until several days before admission when a slight cough productive of thick yellow sputum developed associated with sharp chest pain. This persisted to the time of admission.

FIG. 1. Appearance of skin lesions immediately after death.

Physical examination disclosed an acutely but not severely ill elderly white female with moderate dyspnea. Her temperature was 101.4°F., pulse 132, respirations 32 and blood pressure 160/75. There was a generalized hemorrhagic vesicular eruption over the entire body, including the face, palms and soles, but most marked on the trunk. (Fig. 1.) The lesions consisted of discrete, non-confluent, non-umbilicated vesicles, 0.5 to 1.0 cm. in diameter, separated by normal-appearing skin. The vesicles had a raised purplish base and some were covered with brownish eschars. A few vesicles were present on the tongue, in the right external auditory canal and on the conjunctiva of the left eye, which was injected and tearing. The original lesion over the left eyebrow was small and crusted.

Examination of the lungs revealed dullness, decreased tactile fremitus, diminished breath sounds and moist rales over the right lower chest posteriorly and in the axilla. A few fine rales

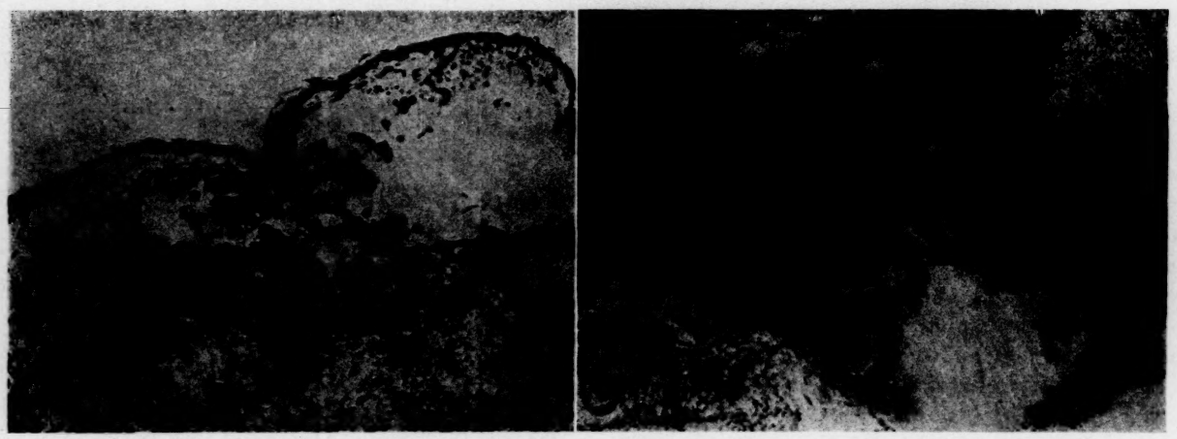

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FIG. 2. Skin lesion showing vesicle formation and detached cells.

FIG. 3. Higher power view of skin lesion showing intranuclear inclusions in many epidermal cells.

were heard over the left base posteriorly. Examination of the heart and abdomen revealed no abnormalities. A few small varicose veins were present on both legs. There was no palpable lymphadenopathy. Neurologic examination was entirely normal and physical examination was otherwise not remarkable.

Laboratory data revealed a leukocyte count of 14,400 with a differential of 3 non-segmented and 70 mature polymorphonuclears, 22 lymphocytes, 3 monocytes and 2 eosinophils. On the smear the red blood cells appeared normal and the platelets appeared adequate in number. A Mazzini test was negative. Serum non-protein nitrogen was 87 mg. per cent. A blood culture was sterile. Cultures of the sputum and nose and throat grew out Streptococcus viridans, Neisseria catarrhalis and Staphylococcus albus.

No definite diagnosis was made and no specific therapy was given. About twelve hours after admission severe dyspnea rapidly developed and cyanosis appeared. Examination revealed numerous coarse rhonchi over the entire chest. The blood pressure fell to 90/0 and peripheral pulses became unobtainable, but the temperature remained at about 101°F. With oxygen the patient showed temporary improvement but then lapsed into coma and died within a few hours.

Necropsy (No. 9014) was performed three hours after death. External examination was completely unremarkable except for the presence of the skin lesions already described. Microscopic examination of several of the skin lesions revealed changes involving all layers of the epidermis and, to a lesser extent, the dermis and the subcutaneous tissue. There was marked swelling of the squamous epithelial cells, chiefly in the prickle cell layer, and many multinucleated giant epithelial cells were seen. Among these cells were fluid-filled cavities that became confluent in some places to form the grossly visible vesicles. (Fig. 2.) These intercellular spaces contained many detached free-floating cells. Very little leukocytic reaction was present. There was slight hyperemia and edema of the subcutaneous tissue and dermis and scattered small collections of lymphocytes, but no polymorphonuclear leukocytes were seen.

Numerous intranuclear inclusion bodies were present. These were located within apparently intact as well as altered epidermal cells, including the giant cells. (Fig. 3.) A few were also seen within fibroblasts and endothelial cells of small blood vessels in the dermis and subcutaneous tissue. (Fig. 4.) The inclusions were exclusively intranuclear. They were round, hyaline and eosinophilic, and were centrally located within the nucleus, separated by a narrow, clear zone from a thin peripheral rim of deeply staining nuclear chromatin. Each involved nucleus contained only one inclusion body, which occupied most of the space and caused some nuclear swelling. Inclusion bodies identical to those in the skin were also found in the lungs, spleen, liver, adrenals and tracheobronchial lymph nodes.

Each pleural cavity contained about 700 cc. of clear, amber fluid but only a few cubic centimeters were present in the pericardial sac and

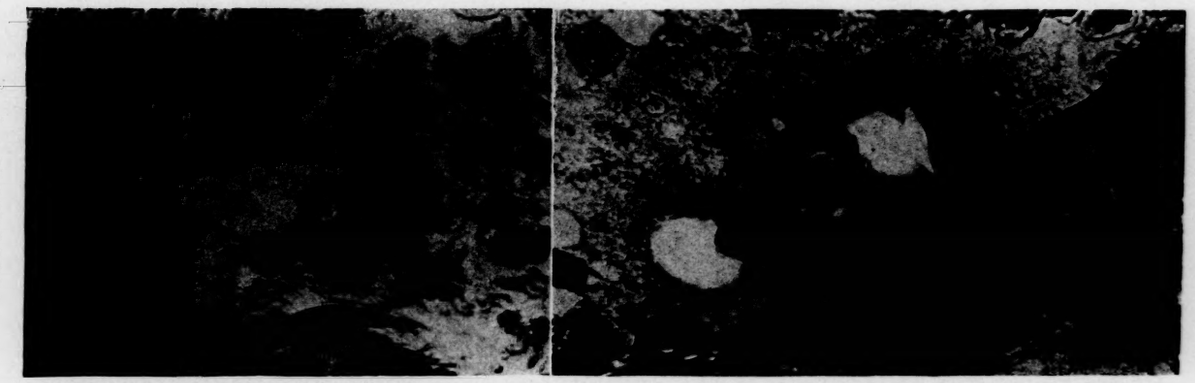

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FIG. 4. Subcutaneous tissue showing intranuclear inclusions in the endothelium of a small blood vessel and in fibroblasts.

FIG. 5. Lung showing alveolar edema and intranuclear inclusions in septal cells and in a macrophage free within the alveolar space.

in the peritoneal cavity. The serous membranes were all smooth, shining and transparent, except for the visceral pleura to be further described.

The heart showed no gross abnormalities, and microscopic examination was completely unremarkable except for the presence of a small, granulomatous nodule in the epicardium of the left ventricle. This consisted of epithelioid cells with a few lymphocytes and multinucleated giant cells and slight fibrosis. It had the appearance of a typical lesion of Boeck's sarcoid.

The lungs were heavy, weighing about 600 gm. each, and showed diminished crepitation throughout. On the pleural surfaces were seen many small hemorrhagic vesicular lesions, resembling those on the skin. The cut surfaces of the lungs were congested and edematous. Radiating from the hilar areas were greyish white streaks and small, irregularly shaped patches; throughout all the lobes were many tiny, indistinct, gray nodules which were somewhat firmer than the surrounding parenchyma. The bronchi and blood vessels were unremarkable. Only a few large hilar lymph nodes were present.

Microscopic examination of the lungs confirmed the gross impression of congestion and edema. The edema involved the peribronchial and perivascular connective tissues and the interalveolar septa. The walls of some of the latter showed evidence of focal necrosis and there were a few minute hemorrhages together with an exudate consisting almost entirely of fibrin. This material filled some of the alveoli; others contained granular, pink-staining material and in still others there were "hyaline membranes." Only a few lymphocytes were seen in these lesions and polymorphonuclear leukocytes were extremely rare. There was also widespread proliferation of alveolar septal cells, some of which contained intranuclear inclusions. These were identical in appearance with those described in the skin and they occurred also within macrophages free in the alveolar spaces. (Fig. 5.)

There were also numerous granulomas with the morphology of Boeck's sarcoid situated chiefly within the bronchovascular rays. Most of these lesions were fibrotic with relatively few epithelioid cells and lymphocytes, and but rare giant cells. Some of the latter contained Schaumann bodies. Peribronchial and subpleural lymphoid follicles contained sarcoid lesions and some of the bronchi showed mucosal involvement. Intranuclear inclusion bodies were seen within a few of the epithelioid cells of the sarcoid nodules.

Microscopic examination of the enlarged tracheobronchial lymph nodes revealed fibrotic sarcoid lesions. There were also a few small foci of necrosis with intranuclear inclusions in some of the cells near these foci. No other lymph node enlargement was present.

The spleen was moderately enlarged, weighing about 300 gm., and was very flabby but otherwise not remarkable grossly. Microscopic study revealed congestion and many necrotic or fibrotic sarcoid lesions. Numerous reticuloendothelial cells in the pulp and especially within the sarcoid granulomas were found to contain intranuclear inclusions. (Fig. 6.)

The liver was of normal size and appearance. The only gross abnormalities were a few tiny

6 7

FIG. 6. Spleen showing intranuclear inclusions in cells of the granulation tissue of a sarcoid lesion.

FIG. 7. Liver showing intranuclear inclusions in epithelial cells. Necrotic cells are seen at the upper margin of the picture.

hemorrhages in the capsule. Microscopic sections disclosed a few small foci of necrosis, located chiefly in mid-zonal portions of lobules. Small numbers of lymphocytes and a few polymorphonuclears were found in the necrotic areas but there was no fibrosis. In the immediate vicinity of these necrotic foci intranuclear inclusions were present in both hepatic epithelial cells and Kupffer cells. (Fig. 7.)

The adrenals weighed 15 gm. together and showed no gross lesions. The only abnormality seen on microscopic examination was the presence of a small focus of necrosis in the cortex of one of the glands, with intranuclear inclusions in some of the adjacent parenchymal cells.

A few small hemorrhages were found in the wall of the small intestine extending through the entire thickness from the mucosal to the serosal surfaces. Microscopic sections showed merely hemorrhage. The kidneys were small but otherwise grossly normal except for a few small stellate scars on the surfaces and small subcortical cysts. Moderate arteriosclerotic atrophy was evident on the microscopic sections. The brain showed no gross or microscopic pathologic condition. However, microscopic examination of the pituitary revealed a minor degree of perivascular cuffing with lymphocytes in the posterior lobe. The remaining organs showed no pathologic changes except for a moderate degree of arteriosclerosis of the aorta.

The final anatomic diagnosis was: (1) generalized hemorrhagic dermatitis; intranuclear inclusion bodies in epithelial, connective tissue and endothelial cells of skin, lung, liver, adrenal, lymph nodes and spleen; pulmonary congestion and edema; focal necrosis of liver and adrenal; hemorrhages of pleura and small intestine; (2) organizing granulomas (Boeck's sarcoid) of lung, spleen, lymph nodes and pericardium.

Attempts were made to recover a pathogenic agent, either bacterial or viral, but the results were negative. Aerobic and anaerobic cultures of the blood, skin and lung were sterile. Suspensions of affected skin and lung were inoculated on scarified rabbits' corneas, injected on the chorio-allantoic membranes of chick embryos and injected into suckling mice, but no viral effects could be demonstrated. Examination of the skin suspension by electron microscopy failed to reveal elementary bodies.

COMMENTS

The clinical diagnosis of this patient's illness was not clear. Although the original diagnosis was chickenpox, this was questioned at the time of admission to the hospital. The history of the case included certain unusual features. The occurrence of a "pilot lesion" and the hemorrhagic appearance of the rash were quite atypical even though instances have been reported[12] of hemorrhagic lesions in chickenpox due to associated thrombocytopenic purpura. Unfortunately, complete hematologic studies were not obtained in this patient.

Following the patient's sudden and unexpected death it was thought highly unlikely that she had chickenpox although it was generally agreed that some type of infection was present. Certain similarities to smallpox were evident, including the hemorrhagic nature of the rash and the fatal termination. However, the mild

character of the disease until shortly before death and the appearance of the vesicles in successive crops were inconsistent with that diagnosis. Some observers suggested the presence of Kaposi's varicelliform eruption, which not infrequently occurs in elderly individuals and in rare cases proves fatal. Against this diagnosis was the absence of an antecedent atopic dermatitis, which is an invariable predisposing factor in that disease.[13]

The findings at autopsy left no doubt that a virus infection similar if not identical to chickenpox was present. The microscopic appearance of the skin lesions corresponded very closely to the classical descriptions[6] of that disease, including the presence of Cowdry's Type A intranuclear inclusions. The failure to recover a virus by animal or chick embryo inoculation was not unexpected and, indeed, served as indirect confirmatory evidence. The herpes simplex virus, which produces a similar pathologic picture in the skin, is usually readily demonstrable by the technics employed.

The possibility of herpes zoster remains and cannot be definitely excluded. At this patient's age herpes zoster is certainly a much more common condition than chickenpox. The presence of a pilot lesion above the left eyebrow was suggestive of zoster and the histopathology of the skin was as consistent with that disease as with chickenpox.

Herpes zoster with a painless, generalized vesicular rash is not excessively rare,[14] and virtually any type of visceral symptom may be present in zoster infections.[15] However, the pilot lesion is apparently invariably painful and the subsequent generalized eruption appears in one rather than in successive crops. The visceral symptoms, which may suggest involvement of any organ in the body, have been attributed to reflex nervous mechanisms, and specific visceral pathologic changes have not been demonstrated. In view of these considerations chickenpox seems the more likely condition. In any case, it may be mentioned in passing that many observers[16] believe that herpes zoster and chickenpox represent merely different manifestations of the same disease.

In addition to the changes in the skin which served to establish the diagnosis of chickenpox the significant pathologic findings were focal pneumonia and focal necroses of the liver, spleen and adrenals. Inclusion bodies were demonstrated in all of these sites as well as in vascular endothelial cells and connective tissue cells. Except for the presence of pneumonia, visceral disease was not suspected clinically. It is possible that careful clinical and laboratory investigation of cases of chickenpox might frequently reveal evidence of generalized involvement. Although the number of cases in the literature is too small to come to any definite conclusions, chickenpox pneumonitis appears to be associated with a high rate of mortality. There are several reports[17] on the use of aureomycin in this condition, with inconclusive results. The antibiotic employed in this case, terramycin, was evidently without effect.

The presence of Boeck's sarcoid in the lungs, spleen, pericardium and lymph nodes appears to be entirely coincidental since it is a fairly common subsidiary finding at autopsy. However, the viral involvement of the epithelioid cells of the sarcoid lesions in the lung, as evidenced by the presence of typical inclusion bodies, is of some interest. The etiology of sarcoidosis remains in dispute and there are still some proponents of a theory of virus causation. Recently Lofgren and Lundback[18] have produced some evidence that a mumps-like virus is a causative factor in some cases of sarcoid. However, there has not been any suggestion that a virus of the chickenpox group may be implicated.

SUMMARY

A fatal case of chickenpox in a seventy-one year old woman is reported. At necropsy, in addition to the typical pathologic changes in the skin, lesions were found in the lungs, liver, spleen, lymph nodes and adrenals. Characteristic intranuclear inclusion bodies were demonstrated in all these sites as well as in the granulation tissue of a presumably incidental sarcoidosis.

Acknowledgment: I wish to express my sincere appreciation to Dr. Edward C. Curnen, Jr., of the Departments of Pediatrics and Preventive Medicine, who performed the virus studies and offered great assistance in the preparation of this report.

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(ab.) = Abstract; (CPC) = Clinico-pathologic Conference; (E.) = Editorial

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Subject Index

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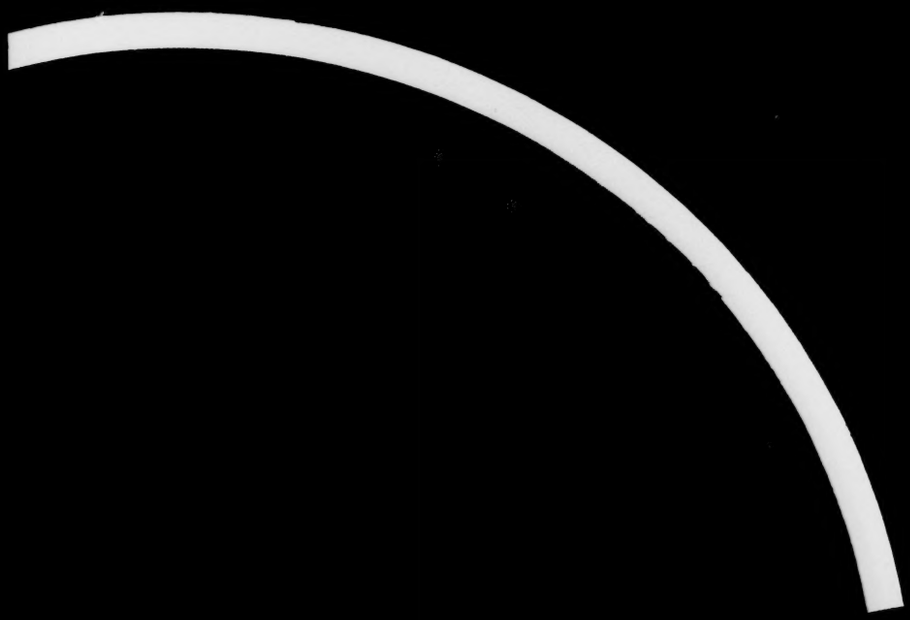

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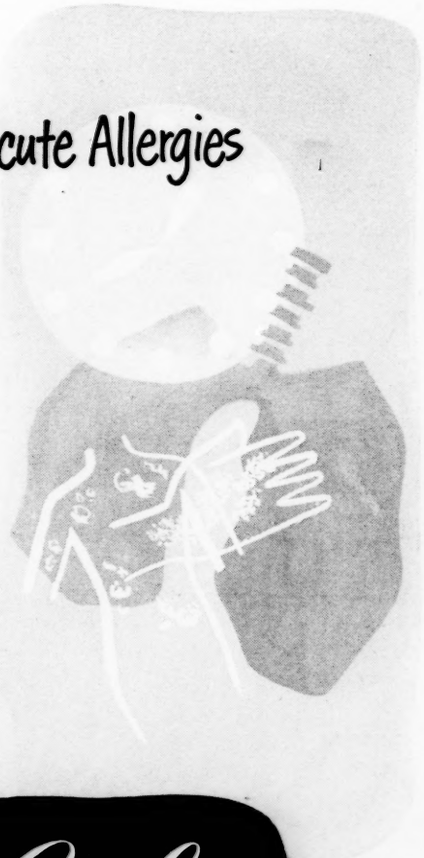

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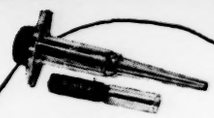

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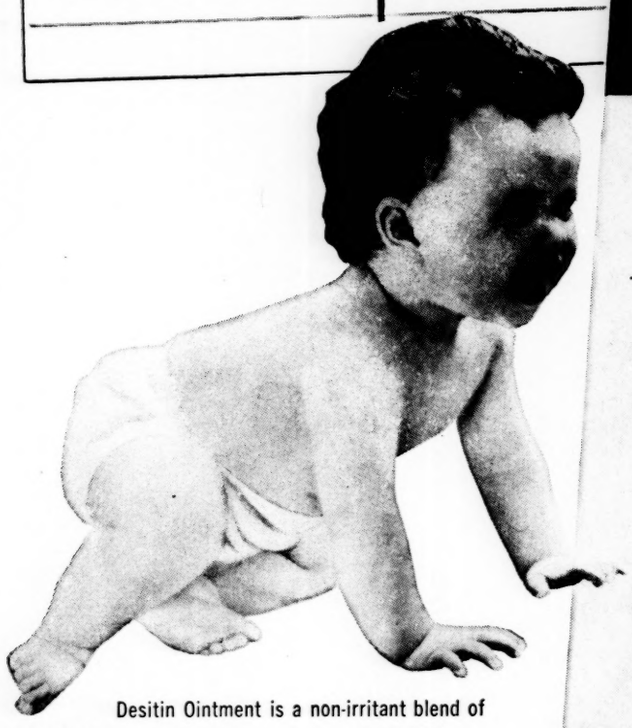

protective — Desitin Ointment "showed definite prophylactic properties" with the incidence of nonsuppurative dermatoses about one-third that of control group.

therapeutic — Desitin Ointment "was used successfully" in the treatment of both non-infectious dermatoses and various infections of the skin in the newborn infant.

in **diaper rash**
- **exanthema**
- **non-specific dermatoses**
- **intertrigo** • **chafing**
- **irritation**

(due to urine, excrement, chemicals or friction)

Desitin Ointment is a non-irritant blend of high grade, crude Norwegian cod liver oil (with its unsaturated fatty acids and high potency vitamins A and D in proper ratio for maximum efficacy), zinc oxide, talcum, petrolatum, and lanolin. Does not liquefy at body temperature and is not decomposed or washed away by secretions, exudate, urine or excrements. Dressings easily applied and painlessly removed.

Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars.

write for **samples** and reprints

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1. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediat. 68:382, 1951.
2. Behrman, H. T., Combes, F. C., Bobrofí, A. and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.

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down

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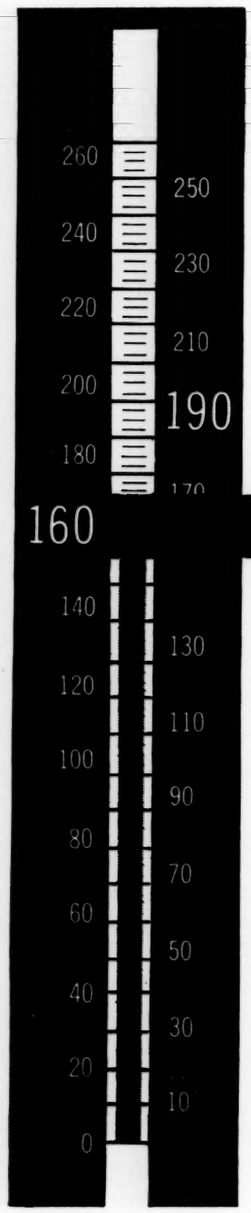
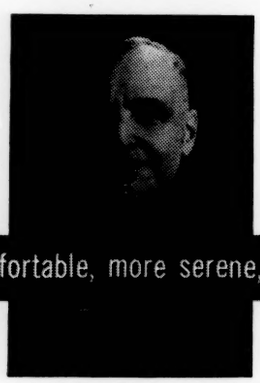


This logical "whole-patient" approach helps the patient on **Pertenal** to live a more comfortable, more serene, often longer life.



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Veratrum Viride (the complex from the whole powdered drug)	100 mg. (1½ gr.)
Homatropine Methyl Bromide	2.5 mg. (1/25 gr.)
Mannitol Hexanitrate	30 mg. (1/2 gr.)
Phenobarbital	15 mg. (1/4 gr.)

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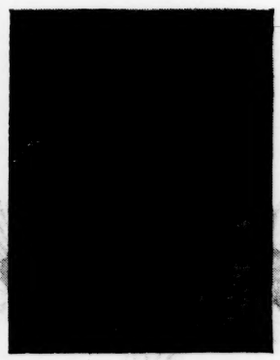

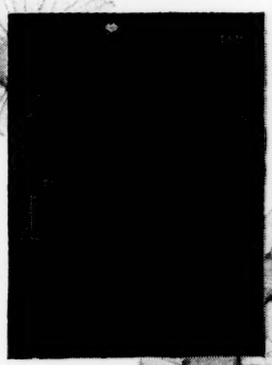

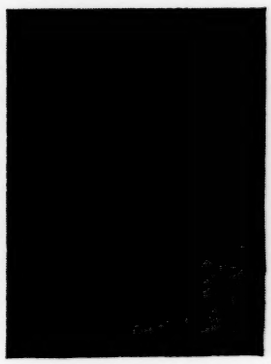

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1. Perloff, W. M.: Am. J. Obst. & Gynec. *58*:684, 1949.

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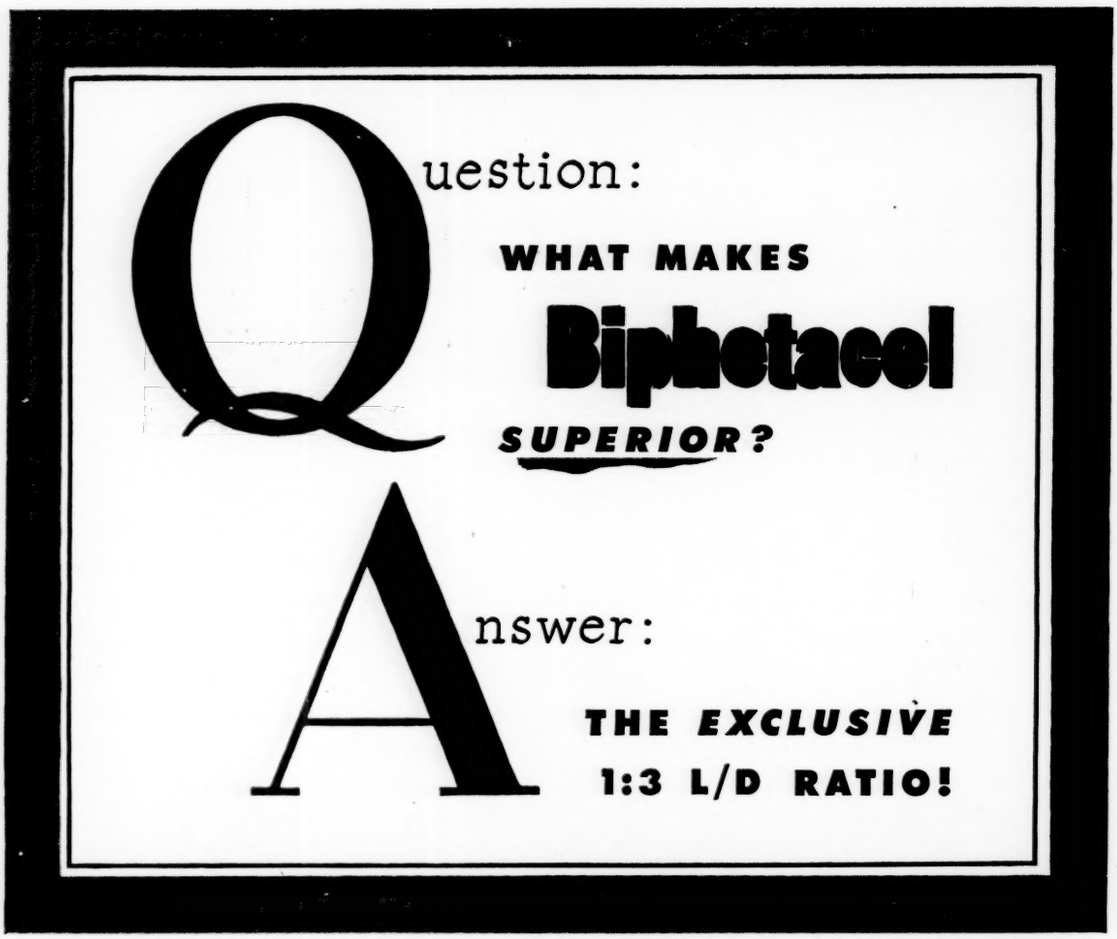

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from the current literature on serum and aortal lipid changes in atherosclerotic hens treated with adenosine-5-monophosphate

Administration of adenosine-5-monophosphate (AMP, MY-B-DEN) to humans had been found to produce marked depression of the serum cholesterol level. On the basis of this observation, and since cholesterol is presumably of major importance in the general problem of atherosclerosis, the authors investigated the effect of AMP in 2-year-old hens in which aortic atherosclerosis spontaneously develops. Treatment lowered serum cholesterol levels and elevated phospholipid values, giving a net increase of 30% in the phospholipid/cholesterol ratio. In addition, the administration of MY-B-DEN caused an increase of 300% in the serum concentration of the S_f 12-20 class of lipoproteins, as determined by ultracentrifugation. Associated with these serum changes were significant declines in the aortal cholesterol concentrations and in the aortal fat content. The decrease in the former averaged 50%. The extent of the atherosclerosis was graded grossly at autopsy. In keeping with the chemical changes in the aortas induced by AMP, it was found that AMP also markedly reduced aortic pathology in atherosclerotic hens.

Milch, L. J.; Redmond, R. F.; Calhoun, W. W.; Chinn, H. I., and Cardiovascular Research Group. Federation Proceedings, Volume II, No. 1, Part 1, page 487, March 1952.

Bibliography 1. Lawrence, E. D.; Doktor, D., and Sall, J.: Muscle Adenylic Acid: A Clinical Study of Its Effect, Angiology *2*:405, 1951. 2. Susinno, A. M.: The Control of Pruritus with Adenosine-5-monophosphate, Am. Pract. & Digest Treat. *2*:491, 1951. 3. Rottino, A.; Boller, R., and Pratt, G. H.: Therapeutic Action of Muscle Adenylic Acid on Ulcers and Dermatitis Associated with Varicose or Phlebitic Veins; Preliminary Report, Angiology *1*:194, 1950. 4. Albaum, H. G.; Cayle, T., and Shapiro, A.: Blood Levels of Adenine Nucleotides, J. Clin. Investigation *30*:525, 1951. 5. Robinson, F., and Hughes, R. A.: Effects of Adenine Compounds on Electrocortical Activity, J. Neurophysiol. *14*:387, 1951. 6. Rottino, A.: Relief from Pruritus Following Upon Administration of Adenylic Acid, Proc. Soc. Exper. Biol. & Med. *71*:379, 1949. 7. Kennedy, R. J.: The Treatment of Pruritus with Adenosine-5-monophosphate (Muscle Adenylic Acid), New York State J. Med. *50*:1609, 1950. 8. Rostenberg, A., Jr.; Brunner, M. J., and Riddel, J. M., Jr.: Failure of Adenosine-5-monophosphate to Affect Favorably Pruritus of Atopic Dermatitis, J. Invest. Dermat. *14*:401, 1950. 9. Sawicky, H. H.; Kanof, N. B.; Hackbarth, D. E., and Marks, I. E.: Assay VI. — Adenosine-5-monophosphate (My-B-Den) for the Relief of Pruritus, J. Invest. Dermat. *17*:265, 1951. 10. Rottino, A.: Effect of Adenylic Acid Therapy Upon Pruritus due to Hodgkin's and other Diseases, Cancer *3*:272, 1950. 11. Rottino, A.: Diagnosis and Treatment of Hodgkin's Disease, Postgrad. Med. *7*:191, 1950. 12. Matt, J. G.: The Treatment of Idiopathic Pruritus Ani with Adenosine-5-monophosphate, South. M. J. *44*:537, 1951. 13. Pelner, L., and Waldman, S.: The Use of Adenosine-5-monophosphate in the Pruritus of Obstructive Jaundice, Am. J. Digest. Dis. *18*:283, 1951. 14. Rottino, A.: The Effect of Adenosine-5-monophosphate on Pruritus, Journal Lancet *69*:285, 1949. 15. Meyer, A. E.: Die Wirkung von Cytochrom, Adenosin-5-monophosphat, Adenosintriphosphat und Adrenalin auf Schlagvolumen und Frequenz des Froschherzens, Arch. f. exper. Path. u. Pharmakol. *213*:154, 1951. 16. Rottino, A.: Adenosine-5-monophosphate in the Treatment of Tendinitis, Journal Lancet *71*:237, 1951. 17. Pratt, G. H.: Surgical Correction of Lymphedema, J.A.M.A. *147*:1121, 1951.

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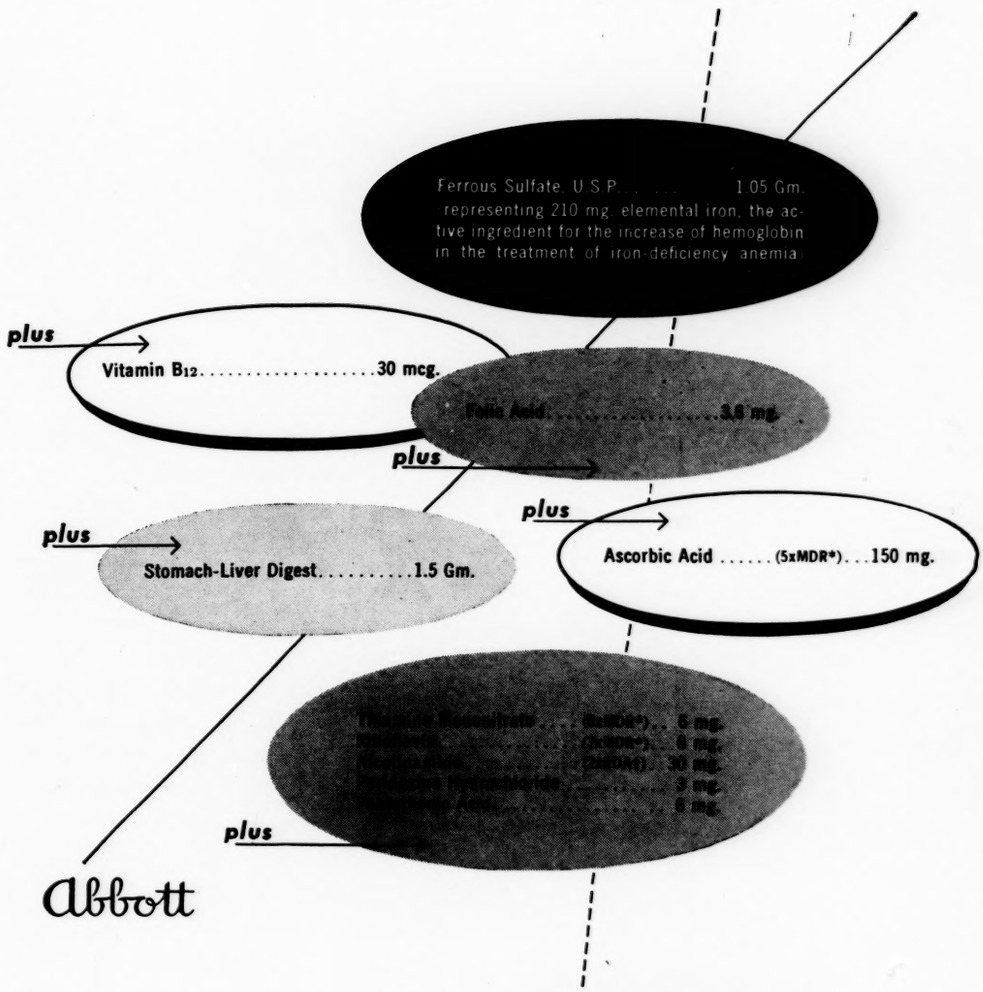

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22 Published Reports Covering Treatment of 1443 Peptic Ulcer Patients with Banthine

Comprising the reports published in the literature to date which give specific facts and figures of the results of treatment

AUTHORS	No. of Patients	Chronic, Resistant to Other Therapy	TYPES OF ULCERS				RELIEF OF SYMPTOMS (Chiefly Pain)				Surgery or Complications[1]	Side Effects Requiring Discontinuance of Drug[2]	EVIDENCE OF HEALING			
			Duodenal	Jejunal	Stomal	Gastric	Good	Fair	Poor	No Report			Complete	Moderate	None	No Report
Grimson, Lyons, Reeves	100	100	93	7			80	11	4		5		47		19	29
Friedman	15	15	14			1	5		4	6[3]			2			13
Bechgaard, Nielsen, Bang, Gruelund, Tobiassen	26	26	21			5	16	4	6				8	6	12	
McHardy, Browne, Edwards, Marek, Ward	162		162				136	12	11		3	1	14	9	7	129
Segal, Friedman, Watson	34	34	34[4]				14	13			7	2	5		8	14
Brown, Collins	117	99	117				97	7	8		5	8	55	9	8	40
Asher	77		65		7	5	52	9	16			16		9	21	47
Rodriguez de la Vega, Reyes Diaz	5	4	5				4		1					3	2	
Winkelstein	116	116	102	8		6	102		14				53		18	45
Hall, Hornisher, Weeks	18	18	18				11		1	6[5]			18			
Maier, Meili	38	38	24			14[6]	27	7	4[7]				10	2	5	21
Meyer, Jarman	25	18	25				21		4							25
Poth, Fromm	37	37	37				33	3	1				33	3	1	
Plummer, Burke, Williams	41	41	41				36		5				38		3	
McDonough, O'Neil	104	100	104				63	10	31			11	4		11	89
Broders	60	60	58		1	1	35	19	6				10	1	49[8]	
Legerton, Texter, Ruffin	11		11				11									11
Holoubek, Holoubek, Langford	76	69	76				35	27	10		4	10	26		10	36
Ogborn	42		39	2		1	42[9]									42
Shaiken	48	48	48				33	10	3		2		33	10	3	
Johnston	145	145	145				143		2			2	143		2	
Rossett, Knox, Stephenson	146		141			5	146					4[10]	53			93
TOTALS	*1443*	*968*	*1380*	*17*	*8*	*38*	*1142*	*132*	*131*	*12*	*26*	*54*	*552*	*52*	*179*	*634*
PERCENTAGES		*67.8*	*95.6*	*1.2*	*0.6*	*2.6*	*81.3*	*9.4*	*9.3*			*3.7*	*70.5*	*6.6*	*22.9*	

1. Not included in tabulations.
2. Included in "Relief of Symptoms" as "Poor" and in "Evidence of Healing" as "None."
3. Four had no symptoms when Banthine therapy was begun.
4. Of which seven were penetrative lesions and five partially obstructive.
5. No symptoms were present in four.
6. Two with symptoms only; no demonstrable ulcer.
7. Three were psychopathic patients and one had a ventricular ulcer of the lesser curvature.
8. Roentgen findings after treatment period of two weeks; forty-seven had duodenal deformity.
9. All returned to work within a week.
10. In these four, after relief of symptoms, Banthine was discontinued because of urinary retention.

During the past two years, more than 200 references to Banthine therapy in peptic ulcer and other parasympathotonic conditions have appeared in medical literature. Of these reports, 22 have presented specific facts and figures on the results of treatment in a total of 1,443 peptic ulcer patients, 67.8 per cent of whom were reported as chronic or resistant to other therapy. These results are tabulated above and show:

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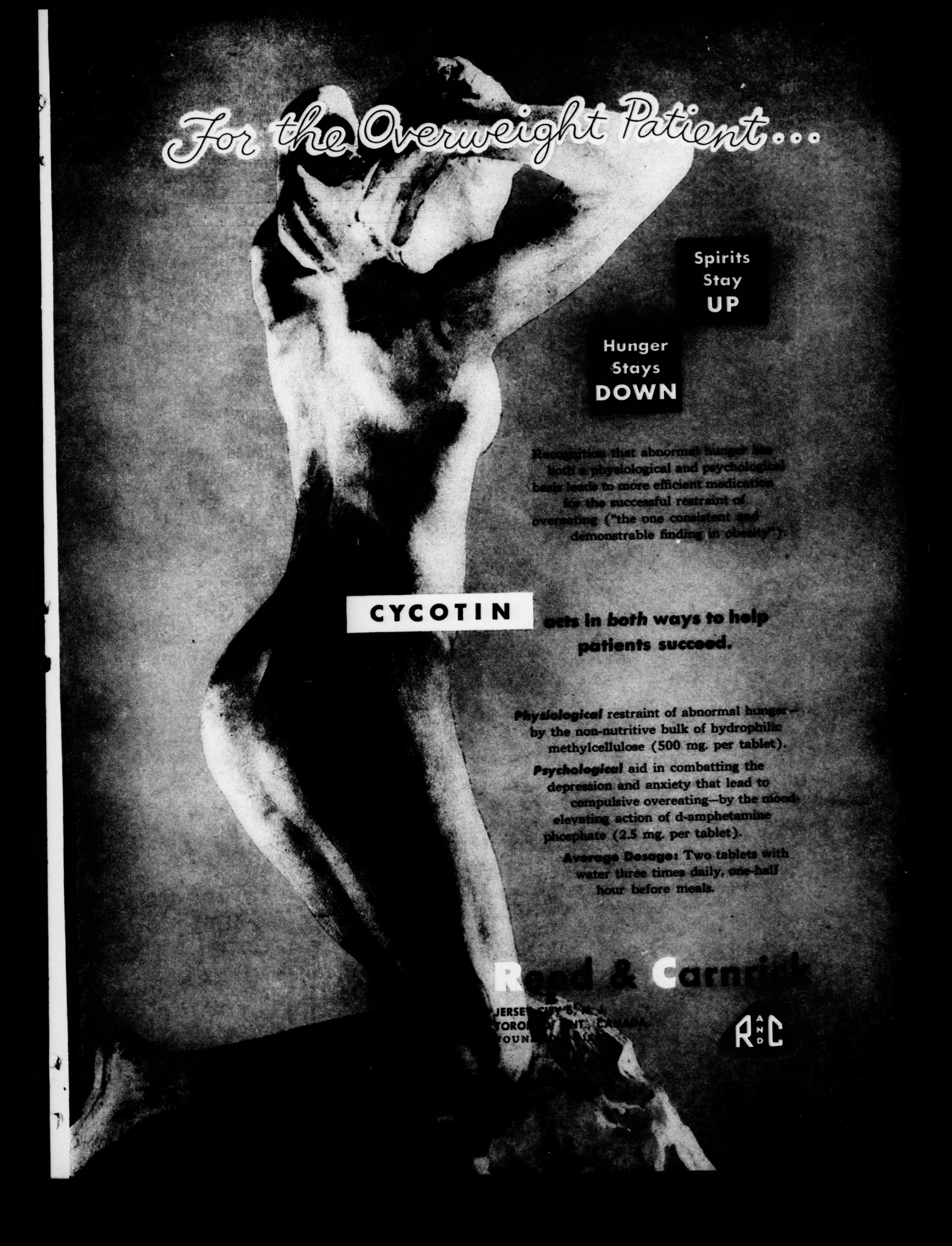
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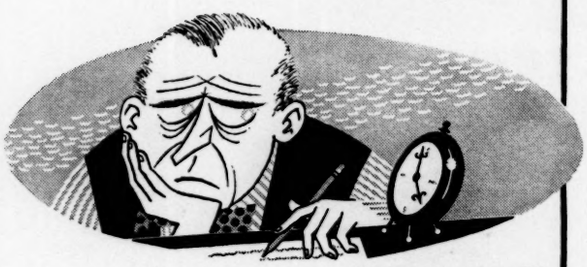

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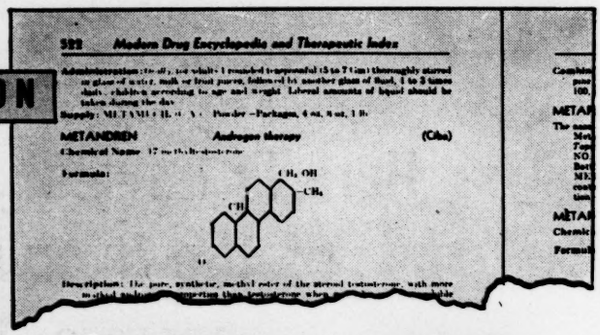

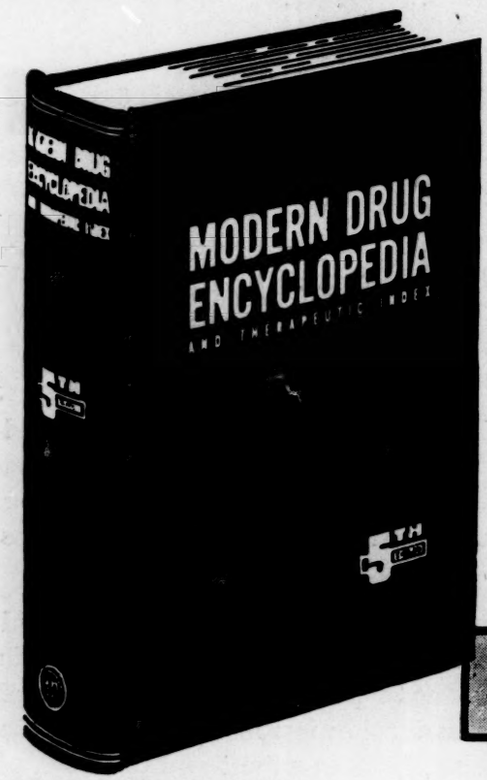

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